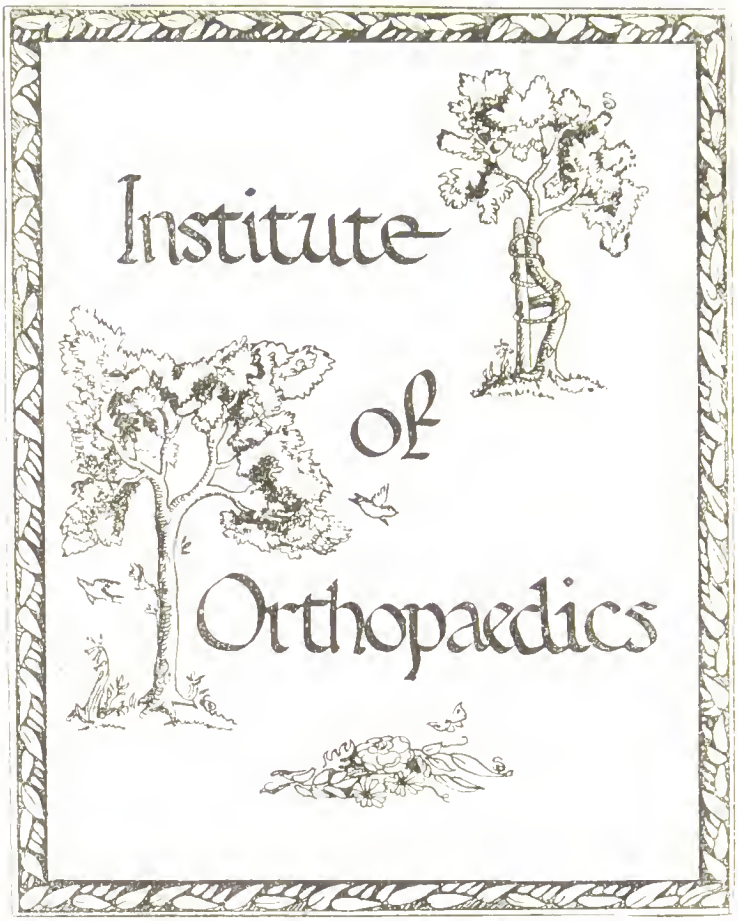
The Degeneration of the Neurone

THE CROONIAN LECTURES
1900

F. W. Mott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THE CROONIAN LECTURES

ON

THE DEGENERATION OF THE NEURONE

Delivered before the Royal College of Physicians of London, on June 19, 21, 26 and 28, respectively, 1900

BY

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London

JOHN BALE, SONS & DANIELSSON, Ltd.

OXFORD HOUSE

83-89, GREAT TITCHFIELD STREET, OXFORD STREET, W.

1900

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THE CROONIAN LECTURES

ON

THE DEGENERATION OF THE NEURONE.

LECTURE I.

Mr. President and Gentlemen,—Allow me to thank you for the great honour you have done me in asking me to give these lectures. I feel the responsibility all the more in lecturing upon the subject I have chosen, when I look back upon the eminent neurologists who have given these lectures on previous occasions. I cannot hope to attain to the philosophy of Hughlings Jackson or the epoch-making researches of Ferrier, but I will endeavour to put before you some thoughts, experiments and observations relating to degeneration of the nervous system which have occupied my attention during the past three or four years.

Definition of the Neurone and the Neurone Theory.

Before considering the neurone under pathological conditions, it is necessary to define the term, to make a few general remarks upon the neurone theory, and to describe our present knowledge of the structure of the neurone. The term "neurone" was introduced by Waldeyer[1] for the nerve cell and all its processes, including the protoplasmic processes or dendrons and the single axis-cylinder process with its cone of origin, its collaterals or side branches, and its terminal arborisation. The theory of the neurone put forward by Waldeyer[1] is that the nervous system consists of innumerable such anatomically independent nervous

[1] *Deutsche Medicinische Wochenschrift*, 1891, Band xvii.

units in contiguity but not in continuity. There is interlacing of the processes, but no nerve network.

The Network of Gerlach.

In 1871 Gerlach,[2] by the gold method of staining, showed an intricate network in the grey matter; he came to the conclusion that the protoplasmic processes of the nerve-cells were all connected in a delicate network, and that out of this network strands of fibrils joined together to form fibres which passed out of the posterior roots and became sensory nerve-fibres. For fifteen years this theory was accepted; then Forel[3] and His,[4] by their studies respectively of degeneration and of the development of the nervous system in the embryo, completely overthrew the doctrine of Gerlach. Forel pointed out the limitation of secondary degeneration; and by the Gudden atrophy method showed that degeneration or atrophy did not pass beyond a cell station when the fibres which arise from those cells are cut through; and he claimed that the nervous system consisted of independent cellular units. Forel also called attention to the remarkable work of Golgi,[5] and although he opposed the diffuse nerve network theory put forward by that authority, yet he recognised the great value of the researches made by his new chrome silver method. About this time Professor His published his researches upon the development of the nervous system, and he showed that the axis cylinder and the other processes of the nerve-cell were outgrowths of the cell protoplasm, and the apparent nervous network was really only an interlacing of innumerable cell processes.

The chrome silver method of Golgi was later adopted by Ramon y Cajal,[6] Retzius,[7] Kölliker,[8] Lenhossek,[9] Van Gehuchten,[10]

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[2] Stricker's "Handbook of Histology," Spinal Cord.

[3] *Einige hirnanatomische Betrachtungen und Ergebnisse, Archiv für Psychiatrie und Nervenkrankheiten*, Berlin, 1887, Band xviii.

[4] "The Nervous System" (L. Barker).

[5] *Sulla Struttura della Sostanzagrigia del Cervello, Gazzetta Medica Italiana Lombardia*, 1873, tomo vi.

[6] Croonian Lectures, *Proceedings of the Royal Society*, 1894. *Vide* Barker's "Nervous System" for later publications.

[7] *Vide* Barker: "The Nervous System."

[8] *Handbuch der Geweblehre des Menschen*, 1896.

[9] *Neurologisches Centralblatt*, 1899, No. 3.

[10] *Anatomie du Système Nerveux.*

and many others, and their researches *apparently* demonstrated the fact that the whole nervous system consists essentially of independent anatomical units, and the neurone theory seemed indisputably established. No matter how multitudinous and complex the branches of the cell might appear yet they never anastomosed with the branches of other cells ; like the trees of a forest there is contiguity but not continuity. Within the last few years, however, owing to the researches of Apáthy,[11], Bethe,[12] Dogiel,[13] and Nissl,[14] there is a tendency on the part of some authorities to go back to a diffuse network theory. Some important researches by Held[15] also have been put forward to disprove the neurone theory. In my opinion, however, one can still accept the neurone theory and admit the truth of Held's observations, namely, that the terminal arborisation of the axis-cylinder process of one neurone forms protoplasmic concrescences by fusion with the cell body and dendrons of another. This, of course, implies continuity of the protoplasm of one neurone with another, but trophically and genetically the two are independent, and it is merely a question of degree of contact of the protoplasm of one with the other. Held agrees with other investigators that in embryonic tissues, and even in early life, the neurones are entirely independent of one another. This independence he can determine by a line of demarcation at the points of contact due to a difference in refraction. This refractive limiting line is, however, not demonstrable in the adult, and he comes to the conclusion that during the process of growth the protoplasm of related neurones fuses. Turner and Hunter[16] by the *intra vitam* methylene blue method, however, come to a different conclusion to

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[11] *Das leitende Element des Nervensystems und seine topographischen Beziehungen zu den Zellen, Mittheilung aus der Zoologischen Station zu Neapel*, 1897, Band xii.

[12] *Ueber die Primitivfibrillen in den Ganglienzellen von Menschen und anderen Wirbelthieren, Morphologische Arbeiten herausgegeben von G. Schwalbe*, 1898, Band viii., S. 95.

[13] *Archiv für Mikroskopische Anatomie*, 1893, 1895, and 1896.

[14] *Nervenzellen und Graue Substanz, Münchener Medicinische Wochenschrift, Deutsche Zeitschrift fur Nervenheilkunde*, 1898, Band xiii.

[15] *Beiträge zur Structur der Nervenzellen und Fortsätze, Archiv fur Anatomie und Physiologie, Anatom. Abtheilung*. 1897.

[16] *Brain*, 1899.

that of Held, for they have shown that the terminal arborisations of the axons of one set of neurones end in a basket work around the cells of functionally related neurones, but do not form protoplasmic connexions.

The neurone theory has always been opposed by Golgi, who maintained that his method demonstrates a diffuse network formed by the collaterals of the axons; but it is especially the work of Apáthy and Bethe which has led authorities such as Nissl to renounce the neurone theory. Lugaro,[17] Lenhossek,[18] Barker,[19] Van Gehuchten, and many other authorities, on the other hand, maintain that the observations of Apáthy and Bethe do not warrant the general conclusion that nerve cells are connected with each other by means of their primitive fibrils. Moreover, Apáthy has only demonstrated a continuous network of elementary fibrils outside the nerve-cells in *invertebrates;* such an arrangement has not yet been proved to exist in vertebrates; in fact, there is the strongest histological evidence that it does not exist. The study of the development of the nervous system and secondary degeneration to my mind shows the genetic and trophic independence of the nervous units; and in spite of the opposition which the "neurone theory" has lately met with in some quarters it is still acceptable.

The Structure of the Nerve-cell as Revealed by the Nissl Method.

The Nissl method is generally used for demonstrating the internal structure of the protoplasm of the nerve-cell and its processes, but before referring to pathological conditions as studied by this method it is necessary to make a few remarks upon the method itself, and the appearances presented by normal nerve-cells.

Nervous tissue, which has been fixed in 96 per cent. of alcohol, formol solution, or corrosive sublimate solution, and of which sections have been cut and stained by basic aniline dyes—*e.g.*, methylene blue, toluidine blue, thionine, and by many other modifications of the original method, shows pictures of the

[17] *Rivista di Patologia*, 1898, p. 500.
[18] *Loc. cit.*
[19] "The Nervous System."

nerve-cells stained in a characteristic manner. If we take as a typical structure an anterior horn cell stained by this method, we shall observe the following characteristics. The body of the cell is stained a deep blue, but not uniformly, for the staining presents a mosaic appearance, due to little stained polygonal areas disposed more or less concentrically round the nucleus and separated one from another by an unstainable substance. Towards the periphery of the cell these polygonal stained areas become elongated, and upon the dendrons they are fusiform, their long axes being parallel to the processes. At one portion of the cell, if it is entire, a process—the axon—will be observed which does not possess any stainable substance, so that we see that this method differentiates two substances—a chromatic stainable substance and an achromatic substance.

Researches to be afterwards alluded to have shown that the stainable substance is a nucleo-proteid, a substance which contains phosphorus, but in less proportion than the nucleic acid of the nucleus, and the fact that the stainable substance is found around the nucleus may indicate that it is a result of the active metabolism of the nucleus on the surrounding protoplasm. By some authorities it is considered to be a store of nutriment, by others a store of energy; and on this account it has been termed by Marinesco "kinetoplasm." The changes which this substances undergoes, as studied by the Nissl method, show that has some important functional relationship to the metabolic activity of the neurone; it is, however, not the essential substance. The unstainable substance, on the other hand, is essential, and consists of an organised network of delicate fibrils which extend into the dendrons, forming a network in the cell substance and passing out again in the axis-cylinder process. Consequently there is probably a direct protoplasmic fibrillary continuity between the dendrons and the axons. This was originally stated to be so by Max Schultze.[20] The nucleus is apparently of simple structure and is permeated by irregular strands of karyo-plasm which form a coarse network; it is apparently situated in the centre of the cell and contains a nucleolus or several nuclear bodies, which, together with the nuclear membrane, stain with a basic dye.

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[20] Stricker's "Manual of Histology."

The Significance of the Nissl Granules.

There is a vast amount of literature concerning the stainable bodies called "Nissl granules." They were at one time believed to be an essential constituent of the living cell, but the researches of Hardy have shown that there is a great difficulty in deciding to what extent structure demonstrable in the fresh or fixed state is the product of the chemical and physical changes which constitute the death changes or due to the action of fixatives. Moreover, Held[21] has shown that the *intra vitam* methylene blue method does not reveal Nissl granules in the cells. The stainable (chromatic or chromophilous) substance, therefore, is probably not present in the living cell in the definite form which we see it when the tissues are freed and stained by the Nissl method. It must not, however, be assumed, therefore, that the method is unreliable as a means of studying the bio-chemical changes occurring in the protoplasm of the nerve-cells, for providing certain precautions are taken, it has proved most valuable in demonstrating functional and organic changes occurring in the nerve-cells as a result of injury of the axon or of toxic substances in the blood.[22]

The large motor cells of the cord and brain are the best for studying the changes in the cell protoplasm, because in these structures the stainable substance appears in normal tissues as if it consisted of formed elements (Nissl granules) in the body of the cell and in the dendrons. I have always looked upon these elements as being due to a death-change of the fluid plasm of the cell whereby the nucleo-proteid substance contained in it is thrown down as a fine precipitate, much the same as myosin is precipitated from myosinogen. If this substance is abundant in the fluid plasm it produces when precipitated these definite forms, because it fills up the spaces of the unstainable intracellular fibrillary reticulum. "Chromatolysis" is the term which is frequently applied to designate the disappearance or disintegration of these Nissl granules, and there may be various

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[21] *Ueber Experimentelle Reizung des Nervenmarks.*

[22] Since the method is a *comparative* one great care must be exercised in practising the same details of method of fixation, cutting, and staining the morbid tissues and the normal tissues with which they are to be compared. Again, it is absolutely essential that the tissues examined should be fresh and free from any chance of *post-mortem* decomposition.

stages of chromatolysis. Usually the process begins at the periphery of the cell and on the dendrons. The stainable substance may be greatly diminished or entirely lost in these situations, or, again, the granules may be seen to consist of fine particles, their definite outline being lost, and in advanced chromatolysis the whole cell may be so affected.

The condition and amount of the stainable substance may be an indication of the functional activity of the cell, and it is conceivable that diminution of the nucleo-proteid colourable substance is the expression of the diminution of the vital interaction of the highly phosphorised nucleus upon the surrounding cell protoplasm. I do not consider that chromolytic changes alone are indicative of cell destruction, for, as I shall show later, most marked chromolytic changes may occur in the cells of origin after section of a nerve and yet the cells may completely recover.

Changes of the cell in form and size may be recognised —*e.g.*, swelling or shrinking, due no doubt to an alteration of the vital osmotic reaction of the cell-protoplasm to its fluid environment; likewise the nucleus may be clear and swollen or shrunken, the nuclear membrane in the latter case being thrown into folds. Very frequently the nucleus becomes eccentric in position instead of being situated in the centre of the cell, and owing to abnormal osmotic relations and protoplasmic change it may even be extruded and this of necessity would cause death of the cell. Another indication of death of the cell-protoplasm is revealed by uniform staining of the whole cell and its processes. It occurs in hyperpyrexia and in the coagulation necrosis resulting from obstruction of the blood-supply for a sufficient length of time to cause the death of the protoplasm.

The importance of the chemical and histological changes occurring in the myelin sheath in degeneration of the nervous system, the difference of opinion as to its origin, and the im-important discoveries which have been made by Flechsig, Bechterew and others with regard to correlation of structure and function necessitate a somewhat full account of

The Myelin Sheath and Nucleated Sheath of Schwann.

Nerve-fibres are of two kinds, grey and white. The grey sympathetic fibres differ essentially from the white fibres by

the existence in the latter of a complex phosphoretted fatty substance lying between the nucleated sheath of Schwann and the axis-cylinder process. The white fibres of the central nervous system differ from the peripheral white fibres by not possessing a nucleated sheath of Schwann. The myelin is probably contained in a neuro-keratin reticulum, and this reticulum is much more abundant in the white matter of the central nervous system than in the peripheral, for Kühne and Chittenden[23] have shown that there is about eight times as much neuro-keratin in the white matter of the central nervous system as either in the grey matter of the central nervous system or the white matter of the peripheral nervous system. In 1884 Weigert introduced his hæmatoxylon method for staining the myelin sheath, and by means of this Flechsig[24] and his pupils were able to show that certain tracts of fibres of the central nervous system were developed earlier than others. This method and its various modifications (Pal, Marchi-Pal and Schäfer) have yielded the most valuable results. The different tracts of the posterior columns of the spinal cord were found to be myelinated at different periods, and it was owing to Flechsig's studies that those of endogenous origin (that is, arising from cells *within* the spinal cord) were differentiated from those which are exogenous (that is, have their trophic and genetic centres in the cells of the posterior spinal ganglia). The practical outcome of this research was the modern idea of the pathology of tabes, for it was shown that the exogenous fibres were alone atrophied in tabes, while the endogenous fibres—viz., cornu-commissural zone of Wesphal[25] and the median oval area of Flechsig—were spared, these tracts having their trophic and genetic centres in cells within the grey matter of the cord. These facts were recognised as being incompatible with the prevalent view that the degeneration was caused by a sclerosis or overgrowth of the glia tissue in the posterior columns, or by vascular changes ; but they pointed especially to a nutritive failure in the trophic and genetic centre by which the outlying projections of the axis-cylinder processes and their myelin

[23] *Ueber das Neurokeratin, Zeitschrift fur Biologie*, 1890, Band viii.

[24] *Ist die Tabes Dorsalis eine system Erkrankung? Neurologisches Centralblatt*, 1890, vol. iii.

[25] *Goldscheider ; Die Bedeutung der Reize fur Pathologie und Therapie im Lichte der Neuronlehre*, 1898.

coverings underwent a regressive atrophy; in fact a metamorphosis of the neurones occurred, the inverse of their development.

Correlation of Function and Myelination.

Again, the researches of Flechsig have demonstrated the different centres of the central nervous system, in which tracts of nerve-fibres have their origin or termination; and it is to the application of this method by Flechsig that we owe one of the most exact, and one of the most valuable, contributions to the structure and functions of the human brain. The method depends upon the fact that there is a correlation between the functions of systems, groups, and communities of neurones and the myelination of their axons; thus, in the brain and the spinal cord of the fœtus, the new-born child, and the devoloping infant, tracts of fibres are myelinated with definite regularity at successive periods of time, indicating ontogenetically their functional and structural development. The myelin sheath appears three or four months after the development of the axis-cylinder process; for example, a bundle of axis-cylinder fibres demonstrable by the Golgi chrome-silver method at the ninth month would not show a myelin sheath until three months or more after birth. When the myelination of a nervous system is complete further information by a study of the condition of the myelin sheath can only be obtained by observations made upon secondary degenerations produced either by disease or experimentally, and to this subject I shall refer later with especial reference to the Marchi method. To return, however, to the process of myelination. In the central nervous system, the afferent projection fibres are myelinated before the efferent, and it is a fundamental principle that bundles of fibres of different physiological functions are myelinated at different periods of time. The whole afferent tract, conducting tactile, articular, muscular and visceral sensations by the posterior columns, fillet, thalamus, and corona radiata, is myelinated at birth. These bundles of fibres have already (while the fœtus was in utero) been exercised in conveying impressions to the appropriate receptive centres in the Rolandic region of the cortex, the stimuli being provided by contact of the teguments with the maternal structures and as a result of reflex movements which commence at quickening; for every movement must necessarily be associated with alterations in tension of muscular,

FIG. 1.—Diagram of vertical section through the brain of a new-born child stained by the Weigert method to show myelination of the fibres. All the parts which are dark contain myelinated fibres. Attention is particularly called to the rather faint deep staining about the central fissure which corresponds to the tactile motor area. It will be observed that the association centres are not myelinated. M.O., medulla oblongata; P.V., pons varolii; O.M.N., oculo-motor nerve; O.C., optic commissure; F.A.C., frontal association centre; C C., corpus callosum; C.F., central fissure; P.A.C., posterior association centre; V.S., visual sphere; C, cerebellum; S.C., spinal cord. It will be observed that the pyramidal efferent system is not myelinated.

FIG. 2.—Diagram of vertical section of the brain of a child aged five months. The greater part of the brain now shows by the staining, myelination of the white matter, thus indicating development of the association centres. F.A.C., frontal association centre; C.F., central fissure; P.A.C., posterior association centre; V.S., visual sphere; C., cerebellum. It will also be noticed that the corona radiata and internal capsule are myelinated.

tendinous, and cutaneous structures, giving rise thereby to kinæsthetic impressions; the relays of neurones which proceed to the cortex forming the afferent projection systems are earliest myelinated, as they are the first to be acted upon by stimuli which excite the nerve terminations in the skin, joints, tendons, and mucous surfaces of the developing fœtus. Moreover, the myelination commences first in those parts of the occipital lobe situated around the calcarine fissure, which we know corresponds to the area of the cortex associated with the function of vision. Thus, as shown in the diagrams, in the new-born child only the lower centres of the spinal cord, medulla, pons, corpora quadrigemina, optic thalamus, and certain areas of the cerebral cortex are myelinated. The cortical areas which are so myelinated are situated around the primary fissures and correspond to areas which are the end stations of the afferent projection systems; for example, the tactile motor area is situated around the fissure of Rolando; the olfactory, gustatory, and auditory around the Sylvian fissure; and the visual around the calcarine (see figs. 1 and 2).

Flechsig has shown that at least two-thirds of the cortex cerebri consist of neurones of association, and according to him (although this does not meet with general acceptation) these association centres possess no neurones belonging to the afferent or efferent projection systems. In the fœtus of eight months the pyramidal fibres of the motor efferent system are still without myelin, but Ambron and Held[26] have shown by a new method of examining the condition of the myelin, by the effect produced on polarised light, that the motor fibres of the anterior roots are myelinated earlier even than the posterior roots.[27]

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[26] *Ueber Entwickelung und Bedeutung des Nervenmarks, Archiv fur Anatomie und Physiologie, Abtheilung*, 1896.

[27] This method is a very ingenious one, and as it is not generally known I will describe it a little more fully. *Method.*—Held and Ambron take nerves of new-born animals, tease them in normal saline solution, and examine them in the following manner with polarised light. They place the two prisms at right angles and put the nerve in the same line as the "quartz plate," when it gives a purple colour. The myelinated nerve will appear red, orange, or yellow, according to the stage of myelination (red being the most advanced); these are the subtraction colours, whereas non-myelinated nerve and connective tissue give the addition colours violet, indigo and blue. In this way they have examined all the nerves and they have arrived at the conclusion

In a second paper Held has shown the important influence stimulus has upon myelination, thus establishing still more fully the correlation of function and myelination. Cats, dogs, rabbits (animals which are born blind) were experimented on in the following way. Light was admitted for varying periods to one eye by opening a lid, the other remaining closed. Examination of the optic nerve on the two sides under the same conditions showed a more obvious myelination on the side exposed to light than on the other. The irritation which might be produced by opening the lid was not the cause of this difference, for an animal which had had the lid opened on one side and not on the other, but which was kept in darkness, showed no difference in the myelination of the two sides. The obvious inference is that transmission of light impulses along the optic nerve had stimulated the process of myelination. This experiment agrees with the observations of Flechsig that a child born at eight months showed at nine months more marked myelination of the optic nerves than a child born at full time. Still there must be a primary innate tendency of the axis-cylinder to produce myelin, for a dog kept absolutely in the dark had, on the eighth day, orange-tinted optic nerve-fibres by the polarisation method, showing that myelination had commenced. Edinger[28] states that the discoveries of Kaes show that the cerebral cortex increases in richness of myelinated fibres for a long time, even to the fortieth year and longer, but diminishes in old age. The correlation of function and myelination is thus proved both by positive and negative results. The myelin appears to be necessary for the functional activity of nerve tracts, at least in animals which possess a nervous system with myelinated fibres, for the development of the myelin along particular tracts

that the peripheral motor nerves are more advaneed in myelination than the sensory nerves at early periods of development. Flechsig, as I have remarked, has shown—and they eonfirm this—that the reverse is the case for the central nervous system. They offer no explanation, but possibly it may be found phylogenetically that in the evolution of speeialised reflex acts in the zoologieal series the motor fibres have acquired first the myelin sheath; or it may be that the sensory bundles are made up of fibres having different functions, and that these are myelinated at different periods of time; again, we know that a large number of fibres entering a musele (Sherrington) are afferent in funetion.

[28] "Anatomy of the Nervous System," translated by Hall, p. 233.

of fibres in the central nervous system proceeds in a manner *pari passu* with the development of function. Atrophy and degeneration of the myelin sheath in pathological processes, whether due to disuse atrophy, or to primary or secondary degeneration, are associated with marked disturbances appertaining to the functions of particular systems, groups, and communities of neurones.

The Histogenesis of the Sheath of Schwann.

This has been studied by many observers, and a paper has recently appeared by Gürwitsch[29] reviewing the work of previous observers and giving his own observations upon this subject. Küpffer,[30] Beard,[31] and Gegenbauer[32] believed that the axis-cylinder is developed from a chain of cells of ectodermal origin arranged in a series. Such an idea would conform with the researches of Apáthy upon invertebrates and is opposed to the axis-cylinder being an outgrowth of a nerve-cell situated either in the anterior cornua or the posterior spinal ganglia. If this hypothesis be true the three constituents of the nerve-fibre—axis-cylinder, myelin sheath, and sheath of Schwann—must be formed by a differentiation of protoplasm of these cells. If, however, it be admitted that embryological, morphological, and experimental researches have demonstrated that the axis-cylinder of a nerve-fibre is a prolongation of a nerve-cell, then the sheath of Schwann is genetically foreign and extraneous to the axis-cylinder; but the question arises, How, then, is the myelin sheath formed? Is it developed by the axis-cylinder, as in the central nervous system where the sheath of Schwann is absent, or is it formed by the nucleated sheath of Schwann? Another alternative is that it is developed by a metabolic interaction of the axis-cylinder upon the protoplasm of the series of mesoblastic cells which are wrapped round it.

Ranvier[33] and his pupil Vignal[34] compared the formation of

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[29] *Die Histogenese der Schwanischen Scheide, Archiv für Anatomie und Physiologie*, 1900; *Anatom. Abtheilung, I und II. Heft.*

[30] *Studien zur Entwickelung-geschichte des Kopfes der Kranioten;* reference to Gürwitsch, *loc. cit.*

[31] *Anatomischer Anzeiger*, 1892.

[32] *Lehrbuch der Vergleichenden Anatomie*, 1898.

[33] *Leçons sur l'Anatomie du Système Nerveux*, 1898.

[34] *Ranvier et Vignal: Sur le Développement des Elements du Système Cérébro-Spinale*, Paris, 1889.

the myelin to the formation of fat within a fat cell. Vignal's description of the process of myelination is as follows: At a particular stage of development, when the nerve-fibre consists of non-nucleated bundles of fibrils, mesoblastic cells migrate into the interior of the fibre and apply themselves closely to single groups. Their cell protoplasm increases in length and in breadth until some of the primitive fibrils are enclosed. The definite intervals in the enclosing sheath, corresponding to the nodes of Ranvier, coincide with the spaces between the ensheathing cells; consequently each internode represents a segment of the *continuous axis-cylinder* wrapped round by a mesoblastic cell. At the same time, according to Vignal, the myelin appears in the cell protoplasm in the form of minute droplets; these become more numerous and run together to form a general thin covering of the axis-cylinder. Vignal does not deny the possibility that the axoplasm may share in the formation of the myelin, but in quite a subordinate manner. The observations of Boveri, which recently have been confirmed by Bethe,[35] show that the sheath of Schwann is reflected inwards at the nodes along the axon; if this be true there is (as in a serous membrane) a parietal and central layer, and between the two the myelin is contained. This would prove Vignal's hypothesis. Gürwitsch has studied the development of peripheral nerves in embryo sheep, fixing the sciatic nerve with Apáthy's solution and employing various staining reagents used by that observer. He came to the conclusions: (1) that the nerve-fibre is a prolongation of the ganglion cell; (2) that the sheath of Schwann arises from the surrounding mesoblast; and (3) that the myelin sheath has nothing in common with the sheath of Schwann, and probably arises only as a product of the metabolism of axoplasm. Time will not allow me to give you more than this very brief outline, and to those who are further interested in the subject I would refer them to an admirable digest on the "Histology and Pathology of the Nerve-cell," by Ford Robertson,[36] or to the splendid new work of Barker on the "Nervous System."

It would take too long here to describe the normal structure

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[35] *Loc. cit.*

[36] "Normal and Pathological Histology of the Nerve-cell," *Brain*, 1899 Part lxxxvi.

FIG. 3.—Diagram to show reflex arc. A, skin with sensory endings; B, Paciuian corpuscle; C, end organ of tendon (Golgi); D, sensory nerve fibres. (Only one sensory nerve fibre is represented as conveying impulses from the three above-mentioned structures, A, B, C, but it must be clearly understood that there are separate neurones for each); E, cell of posterior spinal ganglion with fine granules scattered through the body of the cell; these are the chromophil granules. Emerging from the capsule is the axis-cylinder process forming a T. The central process passes to the spinal cord; at F F, the chain of tubular cells representing the sheath of Schwann ceases; but the axis cylinder process is still covered with myelin; it breaks up at G into a terminal arborisation, which is in physiological connexion with H, the motor efferent neurone. The lower part of the cell is represented showing polygonal granules (Nissl); the upper part of the cell shows a fibrillary reticulum. The granules exist all over the cell and on the dendrons except at the emergence of the axis-cylinder process, but they are not represented in the upper part in order that the fibrillary reticulum of the achromatic substance may be clearly shown. The axon becomes coated with myelin; at F F it acquires a sheath of Schwann on emergence from the spinal cord and terminates at K in the motor end plate.

of the various forms of neurones, but to make myself more clea in speaking of degeneration and the changes which occur in the nerve-cell and its processes, I represent here diagrammatically a spinal reflex arc, showing a sensory and motor neurone (fig. 3). Each portion has a brief description appended, so that I need not detain you further with the details. I would call your attention, however, to two facts, viz.: (1) The difference in the myelin sheath as it surrounds the axis-cylinder process and its fibrils within the spinal cord, as compared with the myelin sheath outside the same—in the latter the axis-cylinder is surrounded by a chain of tubular cells containing the myelin, whereas in the former there is simply a continuous coating of the phosphoretted fat, and (2) the different arrangement and appearance of the stainable substance in the motor and sensory cell.

The Degeneration of the Neurone—Brief Historical Introduction.

New methods of experiment, observation, and technique mark the successive stages in our knowledge of the structure and functions of the nervous system in health and disease. Fifty years ago Waller[37] gave his memorable communication to the Royal Society which was the commencement of our knowledge of the degeneration of the neurone. In his paper, "Experiments on the Section of the Glosso-pharyngeal and Hypoglossal Nerves of the Frog and Observations of the Alterations produced thereby in the Structure of their Primitive Fibres," he pointed out that Günther and Schön had ten years before stated that the primitive fibres at the end of a week after division of the nerve, and when it had lost its irritability, showed changes indicating degeneration; likewise Nasse and Steinrück had described changes following division of nerves. Waller's researches showed that a change took place throughout the whole of the nerve below the point of

[37] "Minute Structure of the Papillæ and Nerves of the Tongue of the Frog and Toad," *Philosophical Transactions*, 1849; "Experiments on the Section of the Glosso-pharyngeal and Hypoglossal Nerves of the Frog," &c., *Ibid.*, 1850.

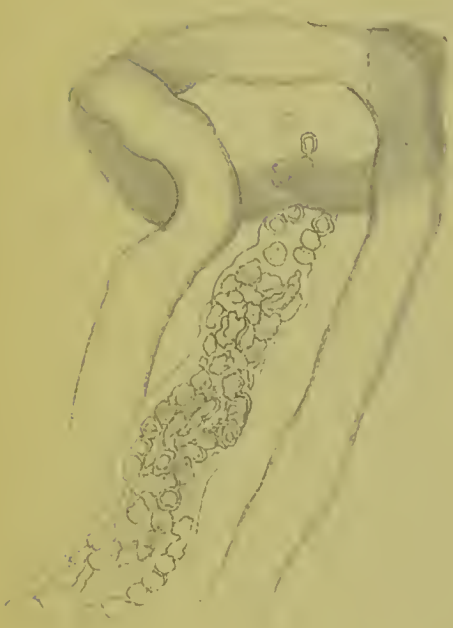

FIG. 4.

FIG. 5.

FIGS. 4 and 5.—Drawings from the original monograph of Dr. Waller (*Philosophical Transactions*, 1850) to show the degeneration of the terminal fibrils of the nerves in the papillæ of the tongue of the frog after section of the nerves. Fig. 4, papillary nerve of frog six days after ligature. Fig. 5, papillary nerve three weeks after section, with muscular fibres in the interior of the capillary coil at the summit of the fungiform papilla.

section, extending to its terminal fibrils. The diagrams exhibit the original pictures taken from Waller's monograph (figs. 4, 5 and 6). He concludes his paper with this very apposite statement: "We cannot suppose that this is a local phenomenon and that the nerves do not participate in similar alterations, and that the brain itself, composed in great part of tubular fibres, must

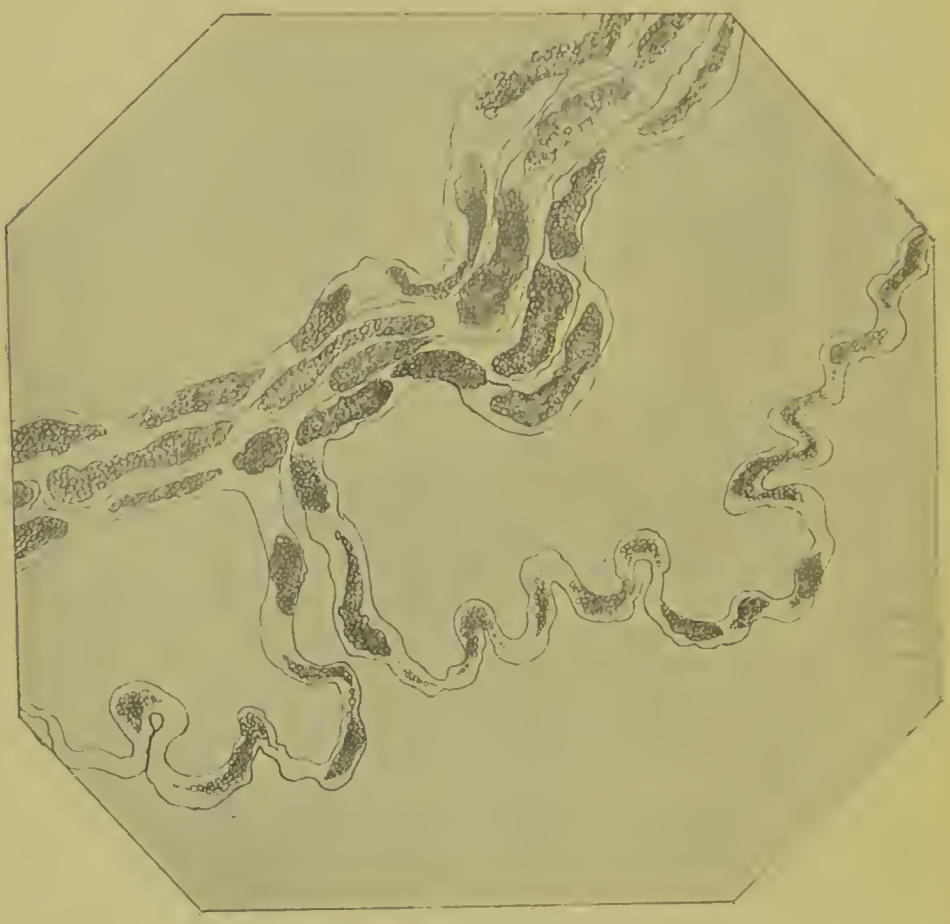

Fig. 6.

Fig. 6.—Disorganised muscular nerve, from the inferior surface of the tongue, five days after section. The muscular fibre has been omitted in this drawing.

be excluded. It is impossible not to anticipate important results from the application of this inquiry to the different nerves of the animal system, but it is particularly in reference to nervous diseases that it will be most desirable to extend these researches." How much light the extension of these researches during the last

fifty years has afforded to neurology can be best appreciated by reviewing the enormous strides which have been made in our knowledge of the anatomy, physiology, and pathology of the nervous system. Waller had anticipated that degenerative processes would be found to occur in the central nervous system, as in the peripheral nerves. He had not long to wait, for in 1852 Türck[38] published a paper showing secondary degeneration of the spinal cord after a transverse lesion, and in 1854 he published his classical paper on secondary degeneration of tracts in the spinal cord and their prolongations in the brain, based upon twenty-one cases. As Waller's observations form the basis of our knowledge of secondary degeneration of the peripheral nervous system, so Türck's observations are the basis of our knowledge of secondary degeneration of the central nervous system. Waller in 1852 extended his researches and formulated the three following fundamental laws which are given in italics in an appendix to the work quoted. The appendix consists of fifty-two important statements bearing upon the results of his experiments.

"As a general rule the sensory fibres develop by starting from the peripheral and radical poles of the ganglion corpuscles and extend from these into the peripheral organs and in the spinal cord to a height undetermined."

"The ganglion corpuscle is in consequence the central organ for the formation and nutrition of its peripheral and central fibres and accordingly we shall call it the neuro-genotrophic corpuscle and the ganglion the neurogenotrophic body."[39] [The neurone doctrine foreshadowed.—F. W. M.]

"Considering the ganglion in its simplest state as a bipolar corpuscle, we are able to assert that every part of the radical and peripheral poles which is separated from the corpuscle disorganises, whilst the whole of the poles in connection with the corpuscle remains normal."

Numerous observers since have claimed that the law for-

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[38] *Akademie der Wissenschaften Sitzungsbericht, Wien*, Band ii., 1854.

[39] *Nouvelle Méthode Anatomique pour l'Investigation du Système Nerveux*, 1852. Waller. His son, Dr. Waller, gives on p. 352 of his "Text-book of Human Physiology" an unpublished drawing made in 1852, illustrating these very points.

mulated by Waller, that every part of a nerve which is separated from its cell of origin undergoes degeneration, *whilst the rest remains normal*, although fundamentally true, may require some modification ; and the first observer whom I find to suggest this is Dr. W. H. Dickinson[40] who, in a very interesting paper on "The Changes in the Nervous System which follow the Amputation of Limbs," stated as a result of his observations that the posterior roots may atrophy, though still in connection with the ganglia, and the anterior though still in connection with the

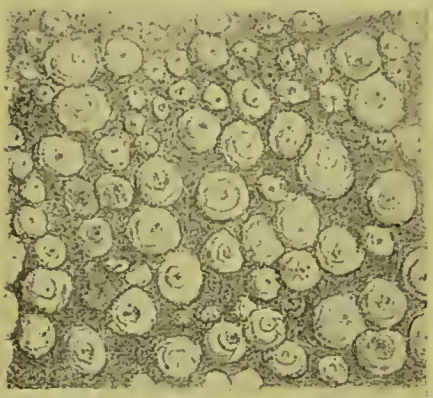


Fig. 7.

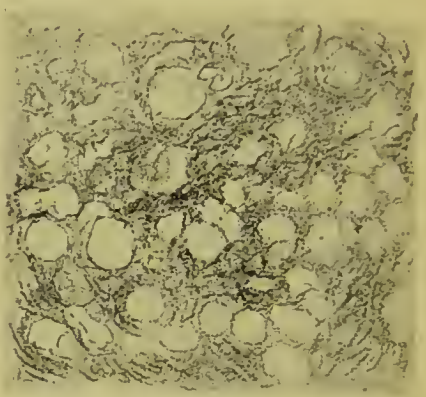


Fig. 8.

Fig. 7.—A transverse section of the normal sciatic nerve magnified 300 diameters. From an article by Dr. W. H. Dickinson, published in the *Journal of Anatomy and Physiology*, November, 1868.

Fig. 8.—A transverse section of the sciatic nerve from the stump of the same person fifty-three years after amputation, also magnified 300 diameters. From an article by Dr. W. H. Dickinson published in the *Journal of Anatomy and Physiology*, November, 1868.

cord ; and it appears that long disuse of a nerve is sufficient to lead to its atrophy, although those nervous structures which immediately regulate its nutrition are complete. (Diagrams here reproduced, figs. 7 and 8.) Bérard in 1839 had noticed atrophy of the central roots in a case of amputation. The degenerations described by Waller and Türck are degenerations *secondary* to injury, and that described by Dr. Dickinson and numerous other observers since may be looked upon as a *disuse atrophy*. A little later Gudden[41] commenced his celebrated work upon atrophy of

[10] *Journal of Anatomy and Physiology*, 1868.

[11] *Ueber die Kerne der Augenbewegungsnerven*, *Neurologisches Centralblatt*, 1882.

the cells of origin of a nucleus by tearing out the nerve in young animals, and this method threw great light upon the anatomy of the nervous system. It was adopted with striking success by Forel and von Monakow.

There is another form of degeneration which, accepting the cellular theory of Virchow[42]—that the whole organism, including the nervous system, is made up of an aggregation of cells, each

FIG. 9.—A transverse section of the cervical part of the spinal cord from a man whose left arm had been amputated twenty-three years before death. The left posterior column (L) is smaller than the right. From an article by Dr. W. H. Dickinson, published in the *Journal of Anatomy and Physiology*, November, 1868. Two circular darker patches in the white matter are accidental imperfections in the picture.

cell being a living unit having an independent existence—is a *primary* degeneration of the complex nerve-cell or neurone. Every cell of the body nourishes itself and is not nourished—that is to say, every cell behaves as a unicellular organism possessing a specific energy; and by the vital reaction of its protoplasm upon the lymph environment metabolic exchanges,

[42] "Cellular Pathology."

constructive and destructive, are continually taking place correlative with functional activity. We have no evidence to show that regeneration of nerve-cells can take place in the higher vertebrates, but there is some evidence in favour of the view that all the nerve-cells of the adult body are present in a rudimentary form at birth. The growth of the nervous system depends not so much upon an increase in number of the nervous units, but

FIG. 10.—Diagram after Ramòn y Cajal to show the ontogenetic and phylogenetic development of a psycho-motor neurone. A, frog; B, newt; C, mouse; D, man. It will be noticed that as the zoological series rises there is an increase in complexity of the neurone and in the multitude of points of contact produced by an increase in the dendrons and side branches of the axon. *a*, *b*, *c*, *d*, *e*, shows ontogenetic development of a psycho-motor cell in the human embryo. The reversal of this process probably takes place in primary degeneration.

in their size by multiplication and complexity of the processes. Cajal (I reproduce his diagram) has shown that this growth in complexity during the process of development is not only true ontogenetically but also phylogenetically (fig. 10). Wallerian degeneration proves that the nerve-cell is the trophic centre, and the embryological researches of His have shown that it is the genetic centre. If then we admit the generally accepted view that the nerve-cell in the higher vertebrates is incapable of

regeneration when destroyed, the corollary is that every nerve-cell of the human body is endowed with a specific durability, whereby in the healthy perfect organism every neurone possesses an equally adjusted vital energy, so that not only is functional equilibrium maintained in the physiological processes of active life but also of decay, the regressive metamorphosis incidental to old age being manifested by a gradual and general enfeeblement of the functions of the whole nervous system. Lucretius says: "When the body has been shattered by the mastering weight of Time, and the frame has drooped, with its forces dulled, then the intellect halts, the tongue dotes, the mind gives way, all faculties fail and are found wanting at the same time. It naturally follows that the whole nature of the 'soul' is dissolved like smoke into the high air, since we see that it is begotten along with the body and grows up along with it, and as I have shown breaks down at the same time worn out with age."[43] In contradistinction to this normal senile decay are premature pathological processes of decay, attacking groups, systems, or communities of neurones subserving special functions, whereby functional equilibrium is destroyed, symptoms of disease are manifested, and according to the functional relations of the system selected characteristic symptoms are presented, constituting clinical groups. The neurones of a particular system die prematurely, owing to an *inherited or acquired want of durability*, and the regressive process of decay may be looked upon as a nutritional failure on the part of the same cells to maintain that metabolic equilibrium essential and correlative to functional activity; consequently, *those parts most remote from the trophic and genetic centre of the complex cell (neurone) degenerate.* The process may be regarded as the inverse of development, the fine collaterals and terminal arborisations being the first to disappear. Dr. Hughlings Jackson[44] in his Croonian Lectures, March, 1884, states: "I have long thought that we should be very much helped in our investigation of diseases of the nervous system, by considering them as reversals of evolution, that is, as dissolutions." Morphologically I conceive that the process of primary degeneration is an evolutional reversal commencing in the struc-

[43] Lucretius, H. J. Monro's Translation, p. 124.

[44] "Post-Epileptic States," *Journal of Mental Science*, October, 1888.

tures latest developed, namely, the myelin sheath and the terminal arborisations and collaterals of the neurone.

Before entering into a detailed account of my own observations upon the degeneration of the neurone, which will occupy most of the other three lectures, I will give a few illustrations relating to the neurone theory as regards the transmission of impulses and certain physiological problems connected with variable resistance to transmission and the spread of excitation.

Every Point of the Central Nervous System is in Physiological, if not in Anatomical, Connexion with every other Point, and Resistance to the Spread of Excitation is Variable.

The nervous system may be said to consist of three systems of neurones—afferent, efferent, and association systems (*vide* diagram, fig. 10). Every excitation can spread over the whole nervous system, but it is difficult to understand how there may be a variable resistance to the spread of an excitation, if we accept the diffuse continuous network theory of Gerlach or of Golgi, or how use may lead to the opening up of paths so that the time occupied by transmission of impulses may be diminished by repetition. Facts seem to show that there is a delay in the transmission of impulses in the passage from one neurone to another in the central nervous system. Does this delay occur at the junction of the terminal arborisations of the axon of one neurone with the dendrons of another? or does the resistance occur in the protoplasm of the cell body?

Bubnoff and Heidenhain found that the strength of stimulus was related to rate of transmission *in the central nervous system*, for on stimulation of the cerebral cortex of the dog, the reaction time is shortened by increase in the strength of the stimulus; whereas *the peripheral nerves* are influenced as regards rate of conduction only to a comparatively trifling degree by the same increase of stimulus.

It would therefore appear that a stimulus passes from the upper neurone to the lower more rapidly when the stimulus is strong than when weak, that is to say, the excitation in the upper neurone must reach a certain intensity before it is capable of flowing over and exciting the next in the series. Is the

resistance to the passage of the impulses in the physiological junction of the upper and lower neurones, or in the protoplasm of the cell-body? According to the neurone theory it would be at the junction.

A stimulus which is insufficient to rise into consciousness may, by repetition, lead to summation, and the opening up of a path (*Bahnung*) by breaking down resistance; thus Urbantschitch has shown that very weak sounds, at first not audible, become so by repetition. This effect can be explained by the stimulus opening up the path to the auditory perceptive centre. The same effect can be produced by an effort of the will and concentration of attention, by which the auditory perceptive centre becomes more excitable. That an excitation may spread over the whole nervous system is not to be wondered at when we consider the length of some of the projection system neurones; for example, the posterior spinal sensory neurones, which have their cells of origin in the first sacral ganglion, extend from the nape of the neck to the sole of the foot. The central projection of the T-shaped process gives off a branch, which extends in the column of Goll the whole length of the spinal axis, and the peripheral portion as a sensory fibre extends to the sole of the foot. It is probable, therefore, that the central projection establishes connexions by delicate collaterals with the grey matter of the whole spinal axis. The reason why excitations do not spread is probably dependent upon the condition of the bio-chemical stability of the neurones. In strychnia and tetanus poisoning the most localised peripheral excitation will cause general muscular spasm; in both toxic conditions the spread is probably due to a bio-chemical change in the protoplasm of the spinal motor neurones to be referred to later, whereby the excitability is greatly increased, and a slight impulse is sufficient to fulminate the whole system of motor neurones. In epilepsy and other paroxysmal neuroses and psychoses it is possible that some altered condition of the blood associated with an inherited bio-chemical instability of certain groups, systems, or communities of neurones may act as a *fulminating agent.* In neuralgia and local hyperæsthesia the slightest general or distant local irritation suffices to produce pain; thus coughing, the vibration of a passing train, or a slamming door may produce pain by the stimulation of the hyper-excitable neurones.

If a skin reflex is increased on one side of the body then sometimes a slight excitation on the normal side is sufficient to produce the crossed reflex, while perhaps the excitation is not

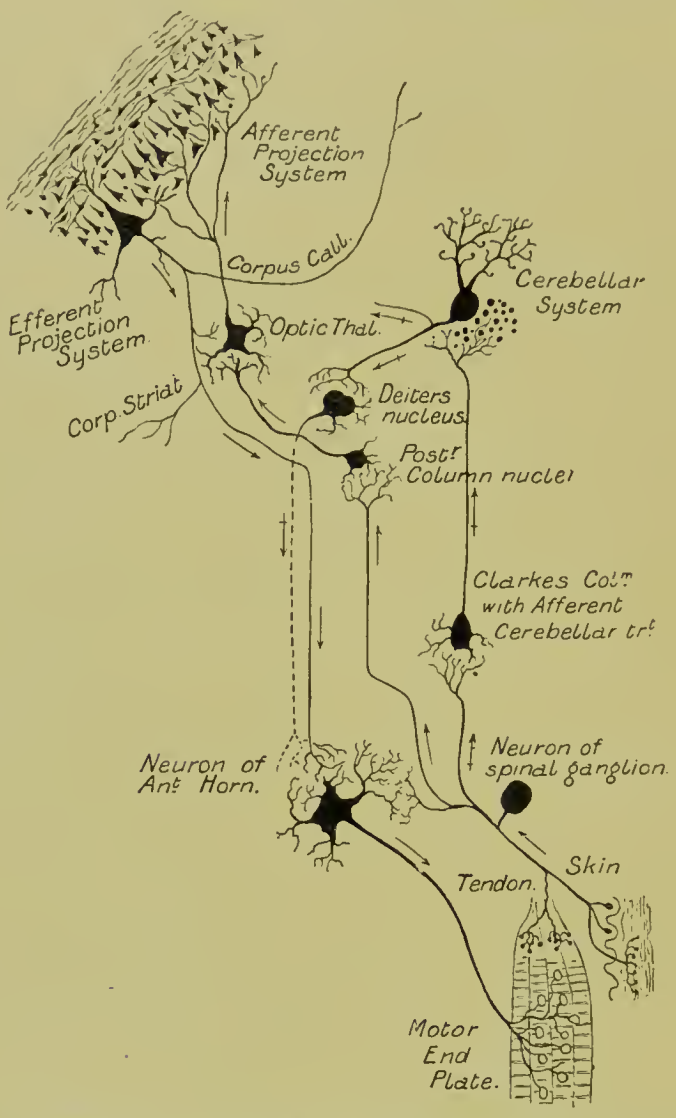


FIG. 11.—Diagram to show the three systems of neurones, illustrating the path of sensory impulses to the cerebrum and cerebellum, the path of outgoing impulses from the brain in a voluntary movement and the association of the afferent and efferent projection systems in the grey matter of the brain. This diagram also illustrates the path of a simple spinal reflex and of a psychical reflex.

sufficient to bring about the normal reflex on the sound side. It sometimes occurs that associated sensations (in part of a painful nature) arise from pressure upon spots, which cannot be

explained upon any known anatomical basis. This condition can be understood only by supposing that certain groups of neurones are in a state of hyper-excitability, and that the neurones which are stimulated have fortuitously opened up the connexion by association neurones, and it has been fixed and made easier by each successive stimulation. The excitation spreads, but it is not of sufficient intensity to arise into consciousness, except in the hyper-excitable area.[45]

Besides hyper-excitability, there may be diminished excitability affecting groups, communities, and systems of neurones having special functions. It will be seen later that this lowered excitability is usually the result of the selective action of various poisons producing either functional depression or degeneration, whereby paralytic or other symptoms of loss of function arise in certain definite functionally related systems of neurones, thus causing correlative groups of clinical symptoms due, on the one hand, to perverted function, or loss of function, and on the other hand, producing other groups of symptoms, as pointed out by Hughlings Jackson to be "due to over-activity of nervous arrangements which are perfectly healthy." This disturbance of the functional equilibration of the neurones may be studied by a consideration of the nervous mechanism concerned in voluntary movement. The diagram shows (fig. 11) that three nervous circles, spinal, cerebral, and cerebellar, are engaged and all three systems of neurones take part, for in every voluntary movement impulses are passing up the afferent channels and down the efferent, and these two systems are brought into physiological harmony by the association systems.

Disturbance of the Functional Equilibration of the Neurones.

The perfection of a voluntary movement is brought about by the association and equable adjustment of systems and communities of neurones presiding over groups of correlated antagonistic muscles in such a way that the desired movement is produced with the least expenditure of nervous and muscular energy. Interference with the functions of any one system will disturb

[45] Goldscheider, *Die Bedeutung der Reize fur Pathologie und Therapie im Lichte der Neuronlehre*, 1898.

the normal functional equilibration that must of necessity exist in the action of the whole. Dr. Hughlings Jackson emphasises the fact that the symptoms of nervous disease are due as much to normal physiological functional activity imperfectly applied as to the actual loss of function occasioned by the disease. He pointed out that in paralysis of the external rectus, strabismus caused less trouble to the patient than the double vision occasioned by the physiological activity of the two retinæ upon which the images were prevented by the paralysis from falling upon corresponding points. Again, the importance of the integrity of one set of neurones having a specific function upon all the rest of the functionally related neurones was strikingly shown in some experiments by Sherrington and myself,[46] for we found that if the upper limb were rendered *apæsthete* by section of a number of the posterior roots (third cervical to third dorsal inclusive) not only was the limb of the animal rendered insensitive, but it was unable to perform the finer voluntary movements ; although stimulation of the cerebral cortex in appropriate regions produced every movement, showing that the efferent path for voluntary movement was still open, but the animal was unable to *ideate* the movement. Another marked effect of section of the posterior roots was the immediate loss of tonus in the muscles, showing that peripheral stimulation is the important reflex agent in its production.

Again, the experiments of Bubnoff and Heidenhain[47] show the intimate relation which exists between the functionally related neurones. They found that a weaker stimulus was required to produce a movement of the limb by faradaisation of the cortex cerebri if the limb were gently stimulated ; thus showing that not only in a movement do impulses pass from the cortex to the periphery, but that each successive movement and alteration in tension of the skin, muscles, tendons, and articular ligaments cause a transmission of *kinæsthetic* impulses (Bastian) from the periphery to the cortical centre with an increase of its excitability ; thus there is a continuous molecular vibration occurring in all these circles, and this is of importance with regard to the

[46] "Experiments upon the Influence of Sensory Nerves upon Movement and Nutrition of the Limbs." *Proceedings of the Royal Society*, 1895, vol. lvii.

[47] *Pflüger's Archiv*, 1884, Band xxvi.

metabolic exchange and nutrition of the neurones themselves; for stimulus is essential to function and bio-chemical action.

In discussing later the changes which occur in motor nerve-cells when their axons are cut we shall better appreciate the changes which take place by remembering that if a muscle is paralysed, changes in tension of the related structures—namely, muscle, tendon, skin, ligaments, &c.,—cannot occur, and that normal succession of kinæsthetic stimuli which travel up the afferent system *pari passu* with the stimuli that travel down the efferent no longer take place. Warrington,[48] indeed has shown that section of posterior roots causes chromolytic changes in the anterior horn cells of the same side, indicating that this loss of stimulus produces a depression of the metabolic functions of the spinal motor cells, a fact quite in accord with the physiological results above described.

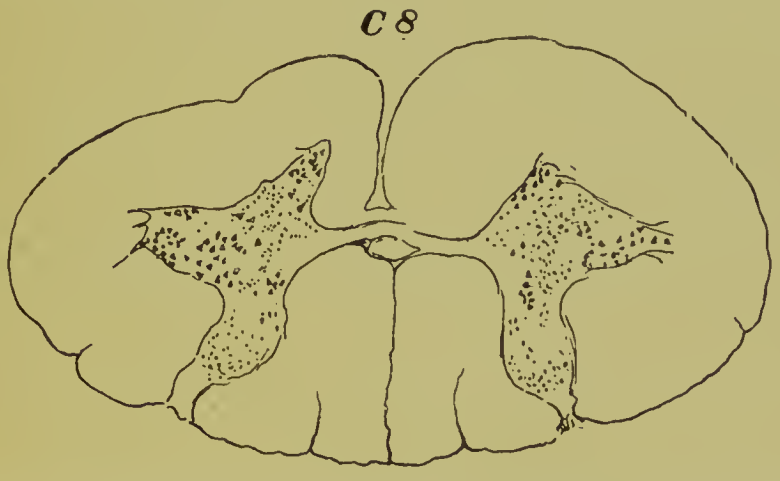


FIG. 12.—Drawing made by means of the Edinger projection apparatus of a Nissl stained section of the eighth cervical segment of the spinal cord, showing a marked diminution of the postero-external and lateral groups of the anterior horn cells. There is a marked atrophy of the antero-lateral region of the cord on the opposite side to the hemiplegia, that is the same side as the brain lesion. The sclerosis of the crossed pyramidal tract on the side of the atrophied anterior horn is not shown.

ANATOMICAL CORRELATION OF ASSOCIATED SYSTEMS OF NEURONES.

The correlation of associated functionally related systems, groups, and communities of neurones finds an anatomical proof in regressive associated atrophy of correlated structures. A good

[48] *Journal of Physiology*, 1898, vol. viii., No. 1 and No. 2.

instance of this has lately been investigated in my laboratory by Mr. Tredgold. Cases have previously been published of a similar nature, but there are some points in this case which have not previously been noticed. The patient suffered from right congenital hemiplegia affecting especially the hand and foot. The lesion was primary in the optic thalamus of the left side; it caused atrophy of the left hemisphere, the right half of the cerebellum, and the spinal motor neurones of the cervical and lumbar enlargements (*vide* fig. 12), descending degeneration of the right crossed pyramidal tract, and of the left antero-lateral tract. We thus see, referring to the diagram (fig. 11), that all the functionally associated efferent tracts of the three nervous circles engaged in voluntary movement had undergone atrophy in consequence of the disuse occasioned by the primary lesion preventing the development of that normal association of correlated neurones necessary for perfect voluntary movement. There are certain very interesting points in this case which will be fully published in the next number of *Brain*.

Additional References.—Hardy: "Structure of Cell Protoplasm," *Journal of Physiology*, 1899, vol. xxiv., No. 2. Alexander Hill: "The Chrome Silver Method," *Brain*, 1896. Tuckett: "On the Structure and Degeneration of Non-Medullated Nerve-fibres," *Journal of Physiology*, 1896, vol. xix., No. 4. G. Marinesco: *Pathologie de la Cellule Nerveuse, Presse Médicale*, 1897.

LECTURE II.

Mr. President and Gentlemen,—In my last lecture I briefly referred to the present position of the neurone theory. I gave some examples of its practical application, and I dwelt at some length upon a method which has been used for studying the bio-chemical changes which occur in the protoplasm of the nerve-cell. Moreover, I pointed out the important evidence afforded by the development of the myelin sheath in proving correlation of structure and function, and that the formation of myelin depends upon three fundamental biological principles: (1) An acquired inherent tendency, the result of evolutional differentiation of structure and function, for certain systems, groups and communities of neurones at successive periods of time to ensheathe their axis-cylinders with an insulating and protecting structure—the myelin sheath which in the case of the peripheral nerves is contained within, and partially formed by, a chain of tubular mesoblastic cells; (2) phylogenetically and ontogenetically considered a stimulus from without is the determining factor in the bio-chemical change associated with the deposition of myelin; (3) absence of stimulus as occurs from long disuse occasions a regressive metamorphosis back to the embryonic type.

The Effects of Injury of the Neurone.

Section of the axis-cylinder or destruction of the nerve-cell (speaking collectively), whether produced by direct trauma or by morbid processes occurring in the vascular and supporting structures of the nervous system, causes a simultaneous death-change of a characteristic chemical nature affecting the myelin sheath and axon extending from the point of injury to its terminal fibrils. This is Wallerian degeneration, or secondary degeneration of Waller and Türck. Ranvier showed that the

sheath of Schwann consists of a series of tubular mesoblastic cells wrapped round the axon, and that when a nerve is cut there is degeneration of the myelin and axon above the lesion as far as the next node. Each internode, therefore, represents a cell, and the fact that the degeneration does not extend upwards beyond the node allows the presumption that these tubular cells have some metabolic interaction with the contained axon and its surrounding myelin. But whatever that reciprocal metabolic interaction of the axon and its ensheathing structures may be, secondary Wallerian degeneration conclusively proves that it is controlled and determined by the nerve-cell and its contained nucleus; indeed, it is possible to conceive that the metabolic activity of the nucleus is the mainspring of this trophic influence, by the production of some bio-chemical or bio-physical stimulus which pervades the whole complex neurone even to its far distant prolongations. The Nissl method has shown that section of an axon causes changes in the nucleus and cell protoplasm. These may be temporary and recoverable or permanent and irrecoverable. The result apparently depends very much upon the degree and extent of the injury. When a peripheral nerve-fibre is cut through, the trophic influence of the cell is removed from the axon and myelin sheath which it generated. These die; not so, however, the independent tubular cells of the sheath of Schwann, for these, soon after the death-change has commenced in the myelin, show signs of active proliferation. Whether, as some authorities would have us believe, they can lead to regeneration of the nerve, or whether, as seems much more probable, they prepare the way for the down-growing axon, I shall not here enter into, but that they have an important function in regeneration is undoubted, seeing that regeneration in the central nervous system, where the sheath of Schwann is absent, does not occur. Tuckett has shown that when a non-medullated sympathetic nerve is cut the nuclei and sheath-like structures remain unaltered, while the axon alone degenerates; it could thus appear that the degenerating myelin may act as a formative stimulus causing nuclear mitosis and cellular proliferation.

The Effects of Injury of a Nerve upon the Cells of Origin.

Only since the introduction of the Nissl method of staining has it become known that changes occur in the ganglion cells almost

immediately after section of the nerve. Nissl, who first studied this, called it "*primäre Reizung*"; and Marinesco, who has made a special study of this subject, has shown that section of the hypoglossal nerve on one side is followed by three stages of change in the corresponding nucleus of origin. The hypoglossal nucleus is especially favourable for the study of this question, the nerve being purely motor. From the close proximity of the two nuclei comparative observations of the nuclei of the two sides make very evident changes, which occur as the result of section of the nerve on one side.

Marinesco divides these changes which occur in the nucleus into three phases. The *reaction* phase occurs during the first month and is characterised by a dissolution of the chromatophil elements and a displacement of the nucleus towards the periphery of the cell. This change has also been recognised by many other observers—namely, Nissl, Ballet et Dutil, Lugaro, Flatau, van Gehuchten, Sano, Erlanger and others. The condition is not necessarily one of degeneration, as I shall show later. It is important to bear this in mind, for a similar condition may be found affecting the anterior horn cells in peripheral neuritis, where disease has led to a destruction of the axis-cylinder process. (Lecture iv.) In the *reparation* phase the cell body increases in volume, the nucleus resumes its original position, and the cell shows a distinct pyknomorphic condition (abundance of stainable substance). About ninety days after the injury the process of reparation has proceeded so far that the nuclear group of the injured side is only distinguished from the uninjured side by the increase in size of the cells and their processes. A little later the cells return to their normal appearance, in point of time corresponding to the regeneration of the nerve. We may consider this cell-hypertrophy as evidence of the increased physiological activity necessary for regeneration. If now the hypoglossal nerve be torn out according to the method of von Gudden, or if a large piece of the nerve be resected, or any other condition arise so severe that the regeneration process in the nerve is prevented, then the reaction phase proceeds rapidly, and instead of a reparation phase of hypertrophy, these cells undergo atrophy, and a *degenerative* phase ensues. The accompanying diagram shows the changes in the cells of the hypoglossal nucleus which result from section of

the nerve in which regeneration is possible; it differs from tearing out the hypoglossal nerve in which regeneration is impossible. In the former case the return of the cells to normal is coincident with regeneration and return of function; in the latter the degeneration and subsequent atrophy of the cell group are brought about by such an injury as to render repair impossible and resembles therefore the effects of amputation of a limb. Recently Schäfer has shown that hemi-section of the

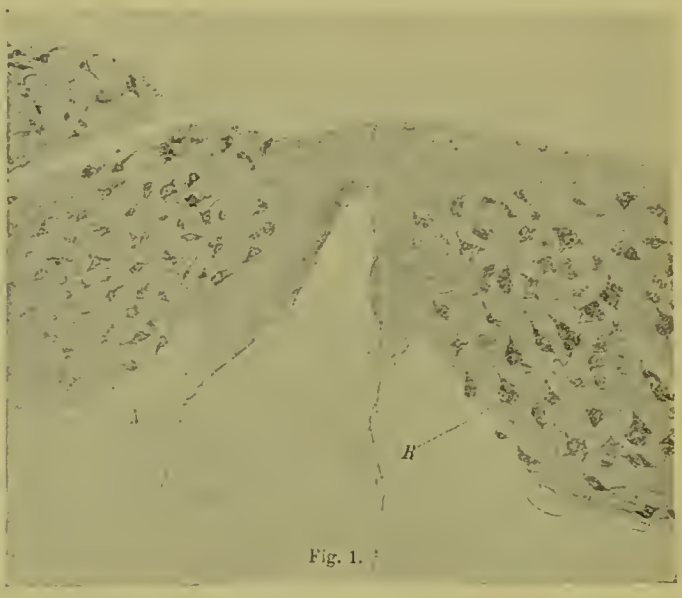


FIG. 13.—Hypoglossal nuclei of two sides. R indicates the swollen cells of the nucleus on the side of section during the phase of reparation. N indicates the normal side. (After Marinesco.)

spinal cord produces chromolytic changes in the cells of Clarke's column and subsequent atrophy, substantiating thereby the theory that these cells give origin to the dorsal and ventral cerebellar tracts, and Lloyd, a pupil of his, has also shown that the cells of Deiter's nucleus undergo similar changes, thus tending to support the observations of Risien Russell, Ferrier, and Turner, that the cells of this nucleus give origin to descending fibres in the antero-lateral region. We can thus see that this method has proved of the greatest value in determining the cells of origin of tracts of fibres. Some observers, Bregmann and Darkschewitz, have even found after tearing out cranial nerves, a degeneration

recognisable by the Marchi method and demonstrating the course of the nerve in the medulla or pons by the black-stained myelin. By the kindness of Mr. Victor Horsley I have the opportunity of exhibiting a lantern slide of the medulla showing degeneration back to the nucleus after an injury made just at the point of emergence of the nerve.

Marinesco, in his admirable work on the effects of amputation, describes slow progressive changes in the myelin sheath, and says the normal refraction of the fat disappears, the colour reaction of the same tends to disappear, and following the changes in the myelin there is a change in the axis cylinder. In addition, there appears a considerable nuclear proliferation of the sheath when the myelin has disappeared, the atrophied fibres bearing resemblance to non-medullated fibres. A recent observation by Noll, which I shall refer to later, showed that the protagon diminished in the central stump of a nerve after section, though, of course, not to such an extent as in the peripheral.

Barker, after referring to the above experiments, as well as to the studies of von Gudden and his pupils and the observations upon the nervous system following amputations, remarks: "We have seen that these observations have partially at least, annulled the validity of Waller's doctrine of the trophic relations of the nerve cells, for after injury to an axon, in addition to the degeneration in the axon, peripheral to the lesion there are demonstrative alterations in the cyto-proximal end of the axon, and especially in the cell body of the neurone itself." The changes which occur after the amputation of limbs are probably, however, due to regressive atrophy from lack of stimulus from the structures over which the neurones presided. The changes which occur in the cells of origin of a nerve after section undoubtedly prove that the whole neurone has suffered by the injury, but there is no evidence to show that a degeneration occurs (in the sense of the chemical change to be referred to later), except in the peripheral portions of the cut nerve and in the central portion as far up as the next node of Ranvier, unless the injury is so severe as to cause such a shock to the neurone that it dies as a whole.

Diseases of the Nervous System as Distinguished from Diseases within the Nervous System.

The histological elements which make up the nervous system may be divided into two groups: (1) the nervous units or neurones; and (2) the supporting, protecting, and nutrient tissues. Organic diseases may start in a primary degeneration of the nervous units or neurones, or the neurones may be affected secondarily by diseases starting in the supporting, protecting, and nutrient tissues. Such are essentially diseases *within* the nervous system and include diseases of the blood-vessels, lymphaties, membranes, and special nerve connective tissue (neuroglia). These give rise to secondary degeneration, either by direct injury, inflammatory compression, or by cutting off the blood supply.

The causes of pathological processes occurring in the nervous system may be considered under two headings—(1) external, and (2) internal; but it may be remarked that in all cases except direct injury the two groups are more or less combined. The external causes depend upon the condition of the blood and lymph by whieh the neurones are nourished and the excess or deficiency of normal stimulation, or existence of abnormal stimulation. The internal causes depend upon the inherent vitality of the neurones themselves. In considering, therefore, the causes of degeneration of the neurone it will be necessary to point out the result of (1) failure of the blood-supply; (2) toxic conditions of the blood; (3) the effect of excess or deficiency of stimulation; and (4) inherited defects in the nervous system as a whole or in some particular groups or systems of neurones. To do this, however, in a satisfactory manner would necessitate my referring in a very superficial manner to all the diseases affecting the nervous system. I shall therefore limit myself especially to personal observations relating to some few causes of the degeneration of the neurone in each of those groups which I have studied.

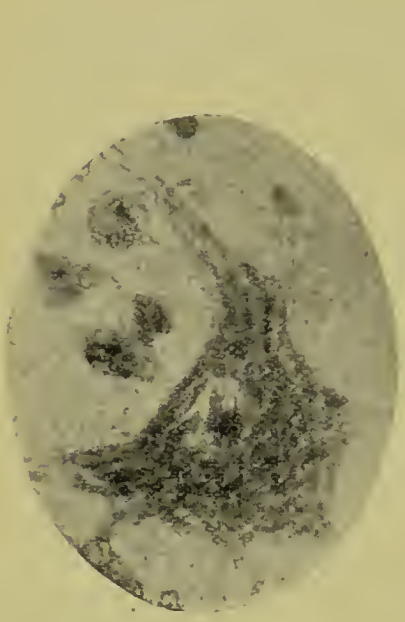
Degeneration of the neurone may be studied by changes in (1) the nerve cell, and (2) the axon and its sheath. By the neurone theory degeneration of the former must be associated with changes in the latter. We have also reasons for believing that degeneration primarily affecting the axon and its sheath

must be associated with functional, if not degenerative, changes in the trophic and genetic centre of the nerve cell.

Effects of Temporary or Permanent Failure of the Blood-supply upon the Neurone.

The effects produced by complete anæmia for varying periods of time upon the nervous elements of the spinal cord have been the subject of numerous experimental inquiries, but I am unaware of any systematic series of observations upon the effects produced by ligation of the cerebral arteries. Many clinical facts show that this is a subject worthy of attention, for the sudden loss of consciousness which results from syncope is explained by a failure of activity on the part of the nervous elements of the cortex cerebri, in consequence of default in the circulation in the hemispheres. Again, the sudden loss of consciousness in epilepsy, followed immediately by tonic spasms and then clonic spasms, has recently found a possible explanation in the series of very valuable experimental observations by Dr. Leonard Hill. He has found that artificial cerebral anæmia in cats or monkeys produced by ligation of the four cerebral arteries produces tonic spasm. If absinthe be injected, instead of causing clonic spasm it increases the tonic spasm. Then, if the clamp or ligature be loosened on a carotid so that blood flows back to the hemisphere, clonic spasms almost immediately occur. This will again give place to tonic spasm on closing the artery; and again on removing the clamp, allowing the blood to flow to the hemisphere, the clonic spasms supervene. He has, moreover, shown that if all four arteries in an animal be ligatured, in the dog recovery takes place; the explanation is that collateral circulation is restored soon enough to prevent destructive changes occurring in the nervous elements. With two carotids and two vertebrals tied the dogs are for some days paretic and demented —very much in the condition of the dogs which Goltz showed after having removed the cerebral hemispheres; however, as Sir Astley Cooper and other observers have shown, these animals recover completely. Dr. Hill has been good enough to send me portions of the brains of twelve such animals operated upon, which after ligation of the four arteries were allowed to live for varying periods of time. I have examined the nervous elements

with a view of determining the condition of the nerve-cells when the dog is in a state of paresis and dementia, and when it has recovered so completely as to pass for a normal animal. The methods which I have adopted have been for this and all other experiments and observations referred to—the Nissl method, the



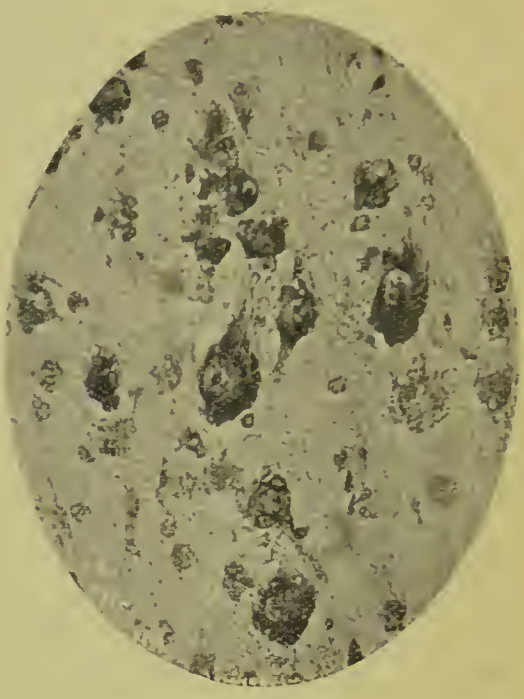


Fig. 14. Fig. 15.

Fig. 14. Normal pyramidal Bett's cell, cortex cerebri, stained by the Nissl method. The preparation was made from the brain of a man who died from an obscure septic affection after eight weeks' illness. Towards the end of life he suffered from severe hæmorrhages, producing the most extreme anæmia, the blood containing a large number of nucleated corpuscles. There was a remittent pyrexia during the whole period; the fever, however, never surmounted 103·5° F. The body was extremely emaciated at death. He remained conscious to the end, and it is interesting that this combination of factors was insufficient to produce bio-chemical changes in the nerve cells. Magnification 700 diameters.

Fig. 15. Section of the cortex cerebri of a dog after ligation of both carotids and both vertebrals. Magnification 250 diameters.

Marchi, the Marchi-Pal, and rapid Golgi methods of staining. The changes observed in the brain by the Nissl method are shown in the accompanying photo-micrographs of the sections (*vide* figs. 15, 17 and 18). Before, however, speaking of the pathological changes, I will again call your attention to the appearances

of the pyramidal cells of the cortex, medulla, and spinal cord of a normal animal when examined by this method, for it is the most reliable we have at present for studying pathological changes by comparing the appearances presented with the normal cells (*vide* figs. 14 and 21). You will observe that, first of all, the cells have changed their shape; they are swollen up,

Fig. 16.

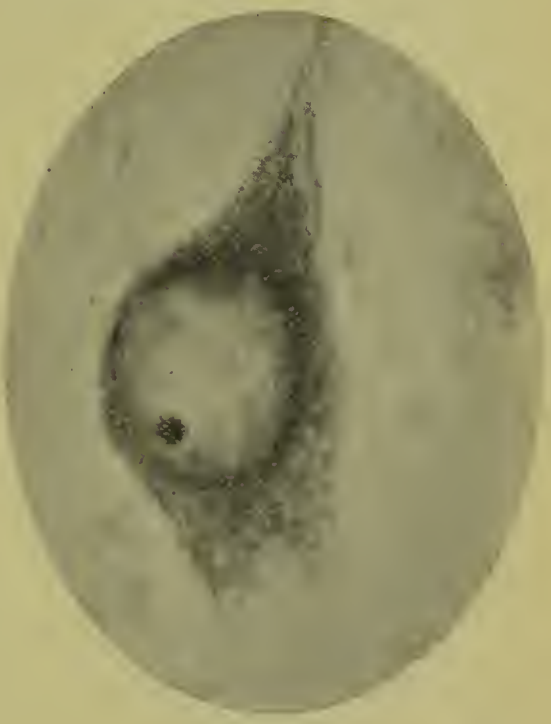


Fig. 17.

Fig. 16. Section of the cortex of a cat that died under the influence of an anæsthetic prior to ligation of arteries. Normal appearance of the cortical pyramidal cells stained by the Nissl method. Magnification 300 diameters.

Fig. 17. Pyramidal cell of a dog after ligation of two carotids, one vertebral and one subclavian. Great swelling of the nucleus, advanced chromatolysis most marked at the periphery of the cell. Magnification 700 diameters.

their edges have not straight or incurved sides, but are curved outwards; the nuclei are swollen and often eccentric, and in some few of the cells may actually be extruded. When this has happened of course the cell has practically been destroyed, and with it the nerve-fibre which contains its axis-cylinder projection. Another obvious sign of change, although not necessarily a destructive change, is the appearance presented by the chromophilous substance. It no longer presents those definite figures

which have received the name of Nissl bodies. Sometimes it appears as a fine dust, sometimes arranged in long threads separated from one another. One of the earliest changes to be observed is the absence or diminution of the chromophilous substance of the dendrons; moreover, the edges of the cells and the processes present a ragged instead of a clear-cut outline. Generally speaking, the changes in the chromophilous substance

Fig. 18.

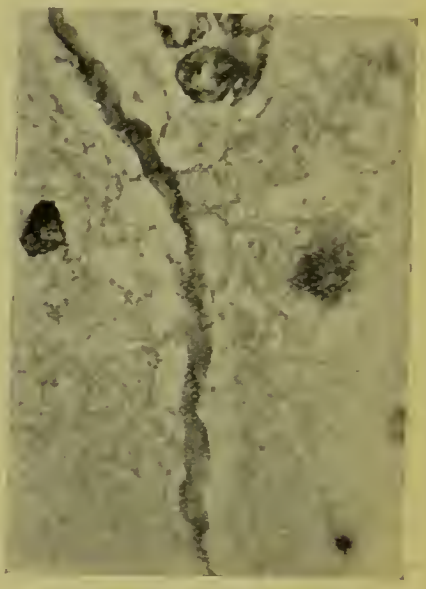


Fig. 19.

Fig. 18. Pyramidal cell of a dog after ligation of arteries, showing extreme chromatolysis with commencing extrusion of the nucleus. Magnification 700 diameters.

Fig. 19. Axis-cylinder process from a large pyramidal cell, the lymph space around which is distended, and showing the collateral side branches apparently forming a diffuse nerve network. Magnification 1000 diameters.

only, do not denote destruction, but should the swelling be so great as to produce an extrusion of the nucleus the cell must necessarily die; and we can, if the animal be kept alive over ten days, determine how many psycho-motor cells have been destroyed by the temporary anæmia occasioned by the ligation of the arteries. We can do this by examining sections of the pons, medulla, and spinal cord by the Marchi method. The

number of black degenerated fibres will indicate the number of pyramidal motor neurones which have perished as a result of the anæmia. These are usually comparatively few. We may consequently say that mere swelling of the cells with very marked chromolytic changes does not mean more than functional disturbance. Mere hydration—for thus I explain the swelling—without dislocation of the nucleus from the cell, even though the chromolytic changes are very intense, does not mean death of the neurone. This is an important fact in view of the association of pathological symptoms with changes in the nerve-cell. Such microscopical changes are for the most part illustrated by figs. 15, 17, 18 and 25. I would add in connexion with this series of experiments that the tangential fibres were found in most cases intact in animals that had completely recovered. We must suppose, therefore, that collateral circulation in dogs is restored very shortly after ligation of four arteries. The experiments of Ehrlich and Brieger in 1884, proved that anæmia of the lower portion of the spinal cord could be produced by ligature of the abdominal aorta, and that if the circulation was cut off for not longer than from a quarter of an hour to three-quarters of an hour, only a temporary paralysis of the hinder extremities resulted; but if for one hour permanent paralysis and destruction of the nervous elements were invariably the result. Numbers of other experimenters have produced anæmia of the lumbar spinal cord by this method; and Sarbo has given a full account of the changes which occur in the cells as a result of complete anæmia lasting for from one hour to one and a half hours after ligation. The changes which he describes as occurring in the motor cells of the spinal cord as the result of complete occlusion of the circulation coincide very closely with the changes which I shall describe in other animals, especially monkeys and cats, also in dogs, which have died as a result of ligation of cerebral arteries, and in which collateral circulation was not soon enough established to prevent destructive changes. Sarbo found that ligature of the aorta for one hour in the rabbit caused a cell degeneration which was manifested by a granular destruction of the stainable substance of the cell protoplasm and a progressive homogeneous atrophic process affecting the cell nucleus. The appearances presented by the degenerating cells depended upon the time which was allowed to elapse between the

ligation of the aorta and the killing of the animal—the longer the time the more evident was the cell destruction. He found no vascular changes indicating inflammation and no hæmorrhages.

The subject of cerebral anæmia is of clinical importance, as it is well-known that in man ligature of a carotid for aneuryism has been followed by hemiplegia, and I have examined the brain in one such case. Dr. Hill sent me a piece of the cortex from similar situations in both hemispheres and asked me to decide by microscopical examination upon which side the patient was paralysed. This I correctly determined by the difference in the appearance of the cells of the two sides. We can understand, also, how *temporary* loss of motor or psychical function—*e.g.*, transitory aphasia, monoplegia, hemiparesis, stupor, and dementia, or even hemiplegia—may occur in syphilitic disease of the arteries; for if collateral circulation be restored within an hour or so after the blocking of the artery, providing a thrombus does not spread to the small branches the circulation may be restored in the part and function may return in the course of a few hours or days.

In connection with the experimental anæmia of the spinal cord produced by clamping the abdominal arteries, it is of interest to note two points. The exogenous fibres of the posterior columns, together with the pyramidal tracts—tracts the fibres of which have their trophic and genetic centres respectively in the spinal ganglia and the cerebral cortex—do not undergo degeneration, whereas tracts which have for their trophic and genetic centres cells in the grey matter of the spinal cord, undergo degeneration. Munzer and Wiener's experiments showed this, and recently I had the opportunity of examining a case of acute anterior poliomyelitis in an infant fourteen days after the onset of the disease. In this case also the degeneration was limited entirely to those tracts the fibres of which arise from cells in the spinal cord, and I cannot help thinking that this case was of vascular origin—possibly spasm of the large artery which comes in to supply the lower end of the spinal cord. Ballet and Dutil found from their experiments that complete anæmia of the lower end of the spinal cord for a few minutes (by clamping the aorta) produced chromolytic changes in the anterior horn-cells. I have also found that swelling of the cells previously described, with chromolytic appearances, may come on within less than ten

minutes after ligation of the four cerebral arteries, for occasionally one of Dr. Hill's dogs or cats has died from the effect of the anæsthetic very shortly after the four arteries have been ligatured. It may be said that this was due to the anæsthetic. It was not, however so, for occasionally I have had the opportunity of examining the brain tissues of animals which have died from the anæsthetic before any of the arteries were tied, and these showed no changes (*vide* fig. 16). We may therefore consider that the changes noted are due to the cessation of the circulation. Dr. Hill has shown that the cortex of these animals is readily excitable, and in some cases even hyper-excitable to, electrical stimulations, epilepsy being produced. Consequently this change in the appearance of the cells can be associated with increased electrical excitability, or, perhaps more likely increased tendency of stimulus to spread—a fact of considerable importance when put beside another fact—viz., that I have found in status epilepticus the cells presenting in many instances this swollen dropsical appearance, with marked changes in the chromophilous substance (*vide* fig. 26). In general paralysis of the insane epileptiform seizures are of frequent occurrence, and when they do occur in the progress of the disease I have found invariably that in proportion to their frequency and severity there is a large number of recent degenerated fibres in the pyramidal systems. Consequently, we may assume that epileptiform seizures in this disease are associated with death of the cortical pyramidal motor neurones, due in some instances (I believe in great measure) to vascular disturbance of the cortex (*vide* fig. 22). The disease itself is, I consider, primarily a progressive decay of the nervous elements, but owing to the establishment of a vicious circle numbers of neurones are destroyed by circulatory disturbances.

I will now pass on to the effects of experimental anæmia, produced by ligature of arteries in which collateral circulation was not restored soon enough to prevent destructive changes in the nerve-cells. If cats or monkeys have all four arteries ligatured, or if, instead of ligaturing both vertebrals and both carotids in dogs, a subclavian be tied instead of one of the vertebrals, a sufficient collateral circulation cannot be restored soon enough and the animal dies in a period varying from a quarter of an hour to twenty-four hours. The time variation

no doubt depends upon the effect produced upon the medulla by the anæmia. The changes observed in the cells of animals which have thus lived some hours are different entirely to those which have been previously described. There is not merely a physical change due to hydration; this may or may not be present, for sometimes the cells are not swollen, but are even shrunken. The staining reaction is also different, showing a bio-chemical as well as a bio-physical change; sometimes the

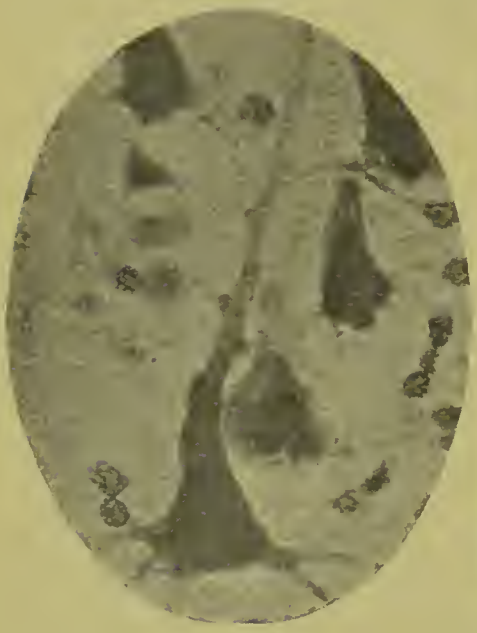


FIG. 20.

FIG. 21.

FIG. 20. Pyramidal cell with diffuse staining from a cat after ligation of four cerebral arteries. Magnification 500 diameters.

FIG. 21. Pyramidal cell from a monkey five days after ligature of two carotids and one vertebral, showing swelling in the pyramidal cell with diffuse homogeneous staining owing to the stainable substance being scattered through the protoplasm of the cell as a fine dust.

whole cell stains uniformly but not with a brilliant colouration (*vide* fig. 20). If a double stain has been used, for example, methyl-blue and saffranine, the whole cell may be stained a uniform dull purple, the processes, as well as the body of the cell, having a homogeneous instead of a differentiated reaction to the dyes—a condition which is similar to that met with in hyperpyrexia and to the appearances described by Sarbo in the motor-spinal neurones of the lumbar-sacral region after clamping the abdominal aorta. These animals prior to death, according

to Dr. Hill's notes, generally had epileptiform convulsions. One animal, a monkey, presented the most instructive changes, because after ligature of both carotids and one vertebral it was paretic and demented, took no notice of anything, and behaved exactly like an animal with its higher cortical centres destroyed, which indeed they were. It was killed on the fifth day, and examination of the brain of this animal exhibited the following

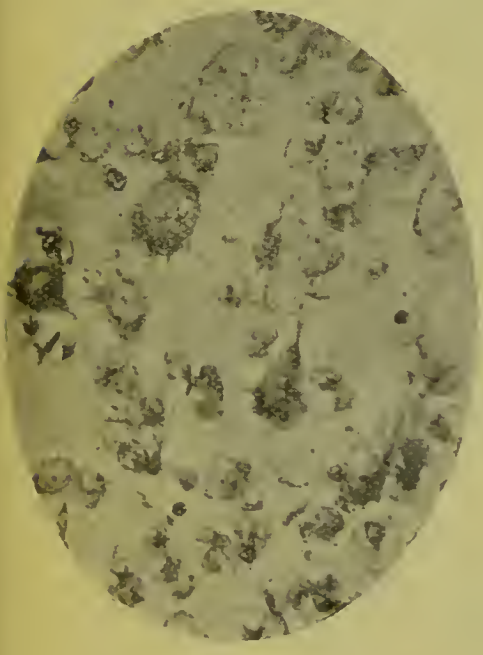


Fig. 22.

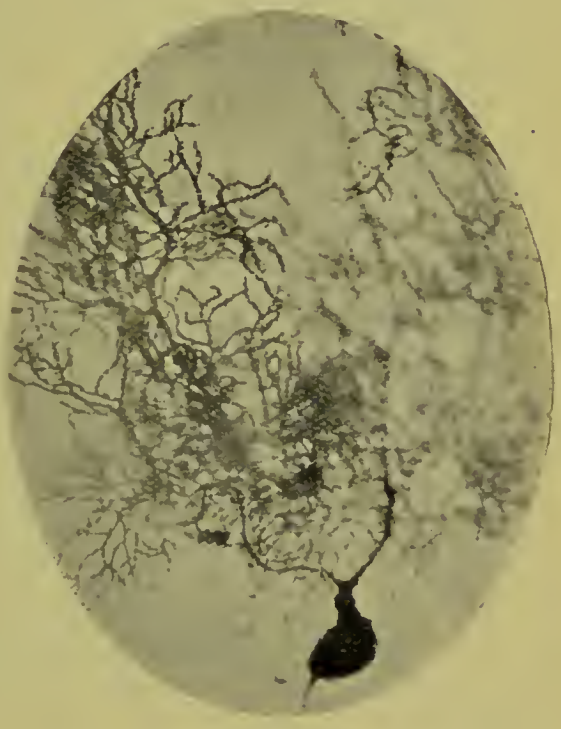


Fig. 23.

Fig. 22. Section of the cortex of a case of general paralysis, showing acute cell changes. Magnification 250 diameters.

Fig. 23. Cell of Purkinje from the cerebellum of a dog twelve days after ligation of four arteries, showing absolutely normal appearances. Magnification 150 diameters.

changes, which are shown in the accompanying photo-micrographs. The nerve-cells and all their processes were uniformly stained a diffuse dull purple and were readily discerned on account of the dilatation of the lymph space in which the neurone lies; scattered through the protoplasm of the cells was a fine dust of coloured particles; the apical processes of the cells were either destroyed or twisted like corkscrews; in many the

dendrites had disappeared, but in some of the cells the axis-cylinder could be traced with unusual distinctness, probably due to some swelling; and one cell was observed which is of interest

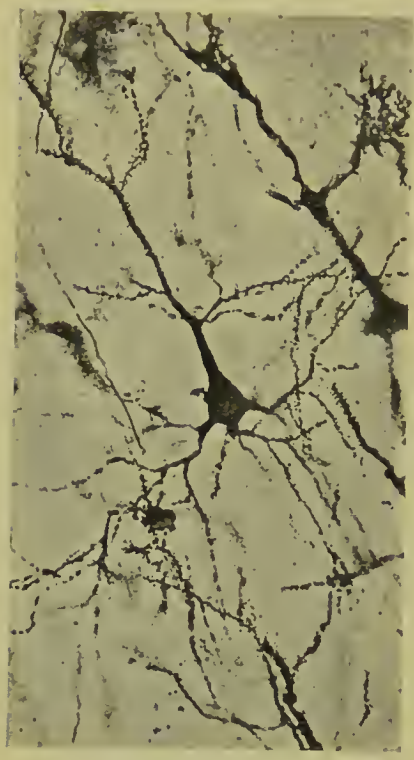


Fig. 24.

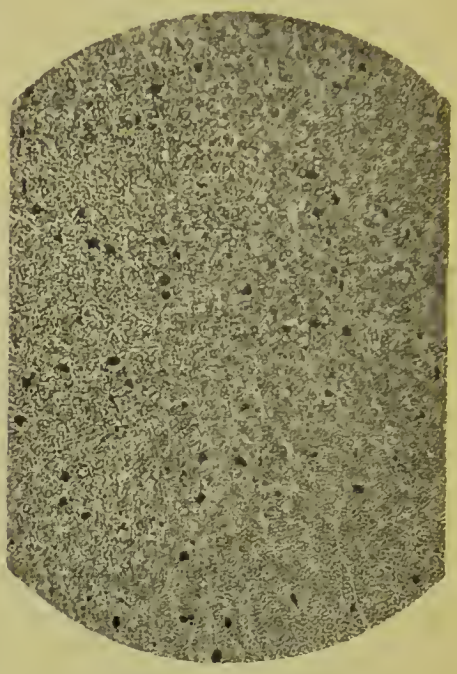


Fig. 25.

Fig. 24. Pyramidal cell from the cortex of a monkey, five days after ligation of two carotid arteries and one vertebral artery. Stained by the rapid Golgi method, showing gemmules on the dendrons and all the external appearances of a normal cell. Magnification 150 diameters.

Fig. 25. Section of the pyramidal tract of the spinal cord of a monkey ten days after ligation of two carotids and one vertebral. A few scattered degenerated fibres are revealed by the Marchi method. These were more numerous on the side opposite to the hemisphere on which the vertebral was ligatured, but altogether they were not more than 60 in number, so that only an inconsiderable number of the psycho-motor cells had perished as a result of the anæmia. This quite conforms with the fact that the animal had returned to the normal physiological condition when it was killed with chloroform. Dogs with four arteries ligatured and kept alive over ten days frequently showed that a certain number of the psycho-motor neurones had perished, but the numbers were inconsiderable.

because the axis-cylinder process could be traced some distance, giving off lateral twigs that seemed to merge into a general network, supporting, therefore, the diffuse nerve network theory of Golgi (*vide* fig. 19). Many of the cells were swollen up, as

fig. 20 shows, and others were shrunken. Some could be seen with phagocytes sticking to them and devouring the dead cells. Although one observed these very marked changes in the cells by the Nissl and Weigert iron methods, yet by the chrome-silver method the cells appeared normal, showing the gemmules on their processes with unusual distinctness (*vide* photo-micrographs 23 and 24). The brains of other animals, dogs and cats, were examined by similar methods with the same results. It may be that the chrome-silver only stained those cells which had not undergone disorganisation; but none of the cells when

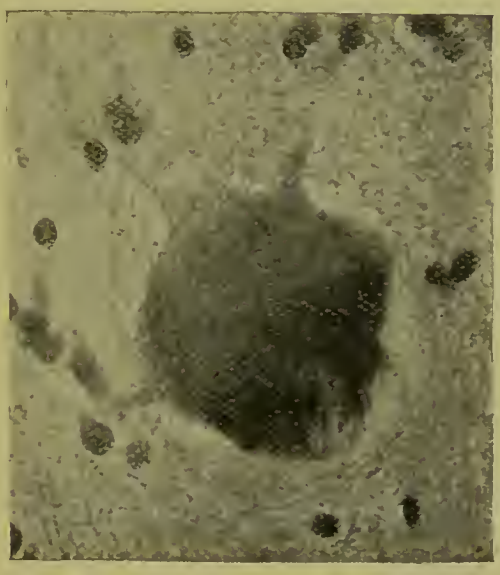


FIG. 26. Swollen œdematous cell from the top of the ascending frontal convolution with diffuse staining and absence of Nissl granules from a case of status epilepticus. Magnification 700 diameters.

examined by the methods I have alluded to exhibited normal appearances as regards their bio-chemical condition, nor was the animal physiologically normal. I have therefore come to the conclusion that the rapid silver method of Golgi which stains only a few cells, although undoubtedly of the greatest value for anatomical purposes, yet for acute pathological findings is unreliable. Many of the statements which are made with regard to the effects of drugs, anæsthetics, and acute disease, as represented by the appearances of the gemmules on the processes of the cells, as made evident by the chrome-silver method, are

therefore open to serious objections. It is very probable that the method of Cox might be found of value in determining changes in the cells of the cortex in chronic disease and possibly also in acute disease. I have not mentioned that in most of these brains experimented on a striking naked-eye feature was the distension of the veins of the cortex with blood, and frequently there was sub-pial hæmorrhage; also the peri-vascular lymphatics were usually distended with fluid. No doubt, both the increase of blood in the superficial veins, the increase of fluid in the peri-vascular lymphatics, and the general œdema of the brain itself were proportional and compensatory to the diminution of the arterial blood. The arteries were generally empty, likewise the capillaries. In some cases the peri-vascular lymphatics and membranes were the seat of a marked cellular infiltration resembling the condition found in general paralysis. Collateral circulation to the medulla, by which the respiratory centre is kept going, is essential to life. Such collateral circulation when established—and if the animal lives it must have been established—would be accompanied by blood-supply to the choroid plexus, and the cerebro-spinal fluid, which functions as the lymph of the brain, would consequently be secreted in abundance and soon compensate for the diminution caused by the failure of the arterial circulation. Thus the increase of cerebro-spinal fluid would account for the œdema of the brain, the dropsical condition of the cells, and the dilatation of the peri-vascular lymphatics.

Some hitherto unpublished experiments which I made five years ago with Professor C. S. Sherrington, and which we have never found opportunity to continue and develop, are, I think, of sufficient importance to mention with this subject of anæmia. We found that compression of the spinal cord in the dorsal region, even enough to produce indentation, would not stop the passage of impulses generated by faradaic excitation of the cerebral cortex to the lower spinal motor neurones. In two animals—monkeys—upon compression with an eye removed from a rat immediately after death, fixed at the end of a glass tube attached to a horizontal lever in such a way that compression of the cord could be made by this living tissue and the pressure measured by means of a sliding weight, we found that *extremely light pressure* upon the lumbar spinal cord was sufficient to abolish conduction

in from one minute to one and a half minutes after the pressure was applied, and upon removing the pressure conduction in a minute or two returned because faradaic excitation of the cortex was responded to by an appropriate muscular contraction. The experiment was repeated a considerable number of times, and I have no doubt that in these two animals we managed to produce an anæmia of the grey matter of the lumbo-sacral spinal cord by compression of the large artery that comes in about the third lumbar root, causing a physiological block in the synapsis formed by the terminal arborisations of the axons of the cortical pyramidal neurones with the dendrons of the spinal motor neurones.

Effects of Hæmorrhage.

Large quantities of blood may be lost to the body from hæmorrhage without producing any appreciable changes in the nervous elements. Voss has performed a number of experiments on animals, endeavouring to produce degeneration of the spinal cord by injections of pyridine sufficient to produce a severe anæmia, but without result. Likewise, numbers of cases of pernicious anæmia, leucocythæmia, and exhausting blood disease are not found associated with any noticeable change in the neurones. I have examined the nervous system in several cases of pernicious anæmia (in one of which the corpuscles had sunk to 500,000 per cubic millimetre), in cases of very severe anæmia from hæmorrhage and exhausting disease, and leucocythæmia (in which the red corpuscles were reduced to one-fourth and in which the whole of the brain and vessels showed congestive stasis and hæmorrhages), and yet the nerve-cells of these cases of extreme anæmia showed little or no bio-chemical change, the Nissl granules appearing quite normal (*vide* fig. 14). Nor did sections of the nervous system in these cases show any degenerative changes by the Marchi method. It is, therefore, more than probable that those cases of combined sclerosis of the spinal cord, sometimes met with in pernicious anæmia, but more often accompanied by grave anæmia, are due to some other cause than the deficiency of red corpuscles. Probably in the blood there is some neuro-toxin which produces this primary systemic degeneration of neurones with long axis-cylinder projections, forming the long tracts in the spinal cord ; or it possibly

may be that those individuals who suffer from this nervous affection have an inherent defective vitality or lowered durability of the nervous system which, in combination with the defect of the blood-supply in quantity and quality, leads to degeneration. The fact that inanition, even extreme inanition, produces little or no loss of weight in the nervous system and hardly any changes of importance in the microscopical appearances of the nervous elements is of considerable importance, for it seems to show that the metabolic exchange which goes on in the nervous system is either especially protected by the metabolism of the whole body being subservient to it, or that however important the metabolic exchange in the nervous system may be, in amount it is not considerable. Those primary wasting diseases affecting systems, communities, and groups of neurones, associated one with another by functional relationship rather than by anatomical or vascular supply, insidious in origin and progressive in course, cannot be essentially due to anything else than a metabolic failure on the part of the neurones themselves (which, after all, are but complex differentiated cells) to assimilate from the blood the necessary materials to maintain their specific vital energy. They die in a manner the reverse of their evolution, the most distant parts of the tree—namely, the terminal twigs (collaterals) —being the first to go, then the branches, and last of all the trophic and genetic centre itself, the cell body and its nucleus.

Dr. Watson in my laboratory has carefully compared the sections of these experimental anæmic brains with a large number of sections of general paralysis. He has made drawings of cells which he considered presented similar appearances in the two conditions, and the result of his observations appears to show that whilst a large number of the cells exhibit changes indicating chronic atrophy, a considerable number of cells in general paralysis present acute destructive changes similar to those met with in cases of experimental anæmia from arterial occlusion, but they are scattered about in small foci. Arteries in this disease are seldom occluded, whereas congestive stasis in the arterioles, capillaries, and veins is common, even thrombosis in the latter may occur ; and we may consider that the destruction of the nervous tissue of the cortex may be accelerated by inflammatory stasis. It is curious how general it is to find the brain atrophy in this disease limited particularly to the frontal and

central convolutions, whereas the occipital and temporal lobes escape in great measure. Over the atrophied regions the pia-arachnoid membrane is thickened and adherent. Many observers, including Flechsig and Mickle, consider that the region of atrophy corresponds particularly with the area of distribution of the internal carotid arteries. I think, however, the area of atrophy and pia-arachnoid thickening more closely corresponds with the distribution of veins which open into the longitudinal sinus, and from a large number of observations made by myself and my assistants I have come to the conclusion that venous congestive stasis in that portion of the brain plays an important part in the symptomatology and pathology of general paralysis. I shall, however, have occasion to refer to this more fully later.

Mendel and many authorities believe that general paralysis is a primary inflammatory condition of the vessels and meninges with secondary destruction of the nervous elements. In 1884 Mendel, who believed that the necessary factors were (1) diseased walls of vessels allowing transudation of plasma and leucocytes, and (2) hyperæmia of the brain, claimed to have produced this condition artificially by rotating dogs upon a table with the heads outwards Fürstner repeated these experiments over a considerable period of time, causing degenerative changes in the cortex, with secondary descending changes in the cord. There are many reasons, however, which will be alluded to later, for considering general paralysis to be a primary progressive decay of the nervous elements with secondary changes in the vessels and membranes.

Altered States of the Blood; Hyperpyrexia.

The study of the lesions of nervous centres due to hyperpyrexia is of great interest from a theoretical as well as from a practical point of view—from the former because the exact knowledge of the nature of the lesion might be able to throw some light upon the nature of the pathological process and the clinical symptoms which accompany hyperpyrexia; from the latter because it would indicate the direction of treatment. Goldscheider and Flatau, who for the first time described lesions of the nerve cells in the rabbit caused by experimental hyperthermia, came to the following conclusions:—(1) If the temperature remained about 106·7° F. the cells of the spinal cord examined by Nissl's method presented no appreciable modifications. (2) If

the temperature exceeded 109·5° F. the lesions of the nerve-cells of the spinal cord were very definite, extending throughout the whole of the grey matter. (3) The duration of the experimental hyperthermia they showed to be a very important factor in the production of the lesions, for if the animal be kept for some hours between 107° and 108° F., the same effect on the nerve cells is produced as occurs in a much more rapid manner when the temperature is raised to 109·5° F.—viz., swelling of the cell and its processes; diffuse staining of the whole neurone with disintegration of the chromophilous substance; and around the nucleus the chromophilous elements still persisting to some extent as if the outer portions of the cell were more affected than the central. The nucleus has an irregular and often an angular appearance.

Marinesco has also done some valuable work on this subject; he found that if artificial hyperthermia in animals be produced, so that the temperature is raised to 116·6° F. in the rectum, the animal died in thirty minutes with characteristic changes in the nerve-cells. He also remarked that these changes occur at a lower temperature when the duration is increased. In five cases of hyperpyrexia occurring in the human subject which I have examined, and in which the temperature reached 109° F. or more, I have found the same bio-chemical change revealed by the Nissl method in all the cells of the central nervous system. I have, however, met with cases of status epilepticus in which the temperature was from 107° to 107·5° F. for a short time without showing this change. Again, I have seen in one case a moderate degree of chromolysis and diffuse staining in prolonged pyrexia varying from 103° to 106·5° F. This was in a case of typhoid fever, and it might very well be that the change was due to the influence of the toxin. In fact, in most of the human cases the changes could be ascribed to the conditions which produced the fever and not to the influence of the increased temperature of the blood. Some of the cases which I have examined, however, were sudden—*e.g.*, one was probable sunstroke, another was a case of hæmorrhage into the spinal canal and the base of the brain in general paralysis, and another was a case of Congo sickness. The photo-micrograph (fig. 27) shows three anterior horn cells from the last case. You will observe the diffuse staining of the processes and of the body of the cell. Another

case of Congo sickness in which the temperature never went above 103° F. showed no change in the Nissl granules and the cells presented a fairly normal appearance. I have examined the nerve-cells in many cases of septic poisoning and other diseases, but I have never seen this change unless there was either hyperpyrexia or prolonged high fever (*vide* fig. 14). The fact that experimental hyperthermia in animals produces this bio-chemical change in the protoplasm of the cell indicates that it is the altered temperature of the blood which is the

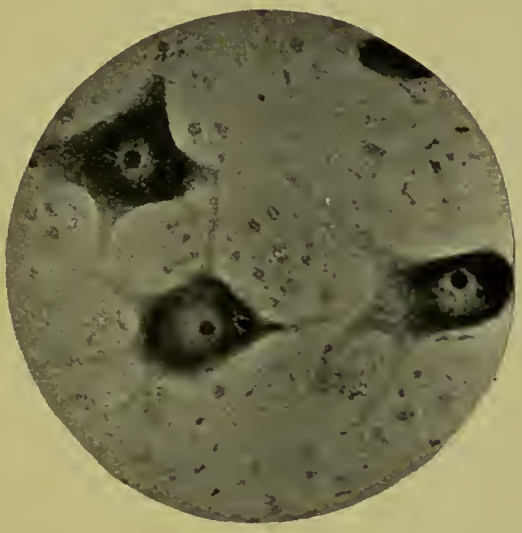


FIG. 27. Section of the spinal cord of a case of Congo sickness with hyperpyrexia in which the temperature reached 109° F. prior to death. The whole of the cells throughout the central nervous system showed a diffuse homogeneous dull staining. The Nissl granules had entirely disappeared from the processes and the body of the cell and the stainable substance had a fine dust-like appearance. The processes are unusually distinct on account of the diffuse staining, the nucleus is clear and swollen, faintly stained, and the nucleolus is deeply stained. Magnification 400 diameters.

cause in the human subject of these changes. Another point is that if the sections are stained with methylene blue and saffranine the protoplasm is stained a uniform dull purple instead of being differentiated. Now we have seen that the healthy cell shows a differentiation of staining; the Nissl granules which have been shown to be a nucleo-albumin are no longer visible in hyperpyrexia; and there is no longer the differentiation of a stainable and an unstainable substance with basic dyes. There must, therefore, have been produced by the fever a profound

modification of the protoplasm of the cell. There are two points to be considered in this—viz.: (1) the fact that a temperature of 109·5° F. can bring about rapidly this coagulation process and death of the protoplasm, also that it affects first and most markedly the periphery of the cell; and (2) that prolonged high temperature of from 107° to 108° F. will produce this same coagulation process.

Halliburton has shown that there are three proteids in nervous matter—viz.: (1) a neuroglobulin which is coagulated at 116·6° F. (47° C.); (2) a nucleo-proteid which is coagulated at 132·8° F. (56° C.); and (3) a neuroglobulin which is precipitated at 167° F. (75° C.)—and that these three bodies can be separated out by fractional coagulation. We see, then, how it is that Marinesco found that animals in which the temperature is raised to 116·6° F. (47° C.) died almost immediately with changes in the cells indicating coagulation in the protoplasm. No doubt this neuroglobulin is precipitated at once, and it occurred to me that if a solution of neuroglobulin were subjected to long heating it would coagulate at a much lower temperature. I mentioned the matter to Dr. W. D. Halliburton, who was of the same opinion, and we have therefore made experiments on this subject, and we find that prolonged heating for four hours, for example, will cause coagulation of the neuroglobulin at a temperature of between 107·6° and 109·4° F. (42° to 43° C.). Moreover, Dr. T. G. Brodie and Dr. Richardson have shown that in frog's muscle the tissue loses its irritability at that temperature at which coagulation is induced first in one of its constituent proteids. We have thus a chemical explanation of the cause of death of the protoplasm, also of the changes manifested by it as regards staining.

Goldscheider and Marinesco have shown experimentally that a certain degree of this coagulation change may take place without death of the cells; for if they produce artificially hyperthermia in animals for only a short time and then kill them they find a commencement of this coagulation process to have taken place. But these animals would have lived had they not been killed for the purpose of examination, consequently we may suppose that a certain degree of bio-chemical change, associated with coagulation of neuroglobulin, may take place without destroying the protoplasm to such a degree as to render

it incapable of recovery. I think this entirely coincides with and explains the remission of symptoms, the return of consciousness, and the recovery which often takes place in some forms of hyperpyrexia when the cold bath method is resorted to without delay.

It is a matter of speculation whether structures later developed and functionally more highly differentiated, as the cells of the cerebral cortex, are more highly susceptible to fever and succumb more readily under it. Possibly high temperature of the surrounding blood and lymph is more readily felt by the small cells of the superficial layers of the cortex on account of the increased surface exposed and delirium followed by coma may be the result of this, although the vital centres in the medulla may still be able to perform their functions.

The diffuse staining of the cells indicates a diffusion of the nucleo-proteid through the substance of the cell body and its processes. We may suppose, therefore, that the essential achromatic fibrillary substance is killed and that the nucleo-proteid which is normally contained in the reticulum of the cell in solution has soaked into the achromatic substance and given the protoplasm the uniform staining which, when once general, is quite characteristic of hyperpyrexial death, as I have been able to verify in several instances. These facts, pointing to an actual bio-chemical change involving the death of the protoplasm when the temperature remains for some hours above 109° F., support Dr. Osler's view that cases of paradoxical temperature occurring in women and termed "hysterical hyperpyrexia" are frauds as a rule, although he states that other cases have to be accepted, the explanation of which is impossible under known rules—in fact, it is quite conclusive that temperature above 114° F. is incompatible with life, even for a short time.

Toxic Conditions of the Blood and Lymph.

The primary degenerative changes occurring in the neurone are usually the result of poisonous conditions of the blood and lymph. The poisons may be produced; (1) within the body by perverted functions of the organs or tissues (auto-intoxication); (2) by the action of micro-organisms upon the living fluids and tissues of the body whereby various toxic substances are produced, either locally or generally, and by their escape into the

blood cause degenerative changes; and (3) the poisonous substance may be introduced into the body from without. Just as we know that various alkaloids used in medicine have a specific affinity for particular portions of the nervous and muscular systems, so we find that certain poisons which produce degeneration and disease have a special selective influence. We know that strychnine, for example, has a special selective influence upon the spinal cord, increasing reflex excitability. Goldscheider and Flatau have shown that strychnine poisoning produces changes in the motor anterior horn cells closely corresponding to those observed in tetanus poisoning; these changes may be observed as commencing three minutes after injection of the poison if a sufficient dose be given. As in tetanus poisoning there is no close relationship between the morphological change and the degree of functional disturbance. These observers have also shown that acute cell changes occur as a result of malonitril poisoning ($NC—CH_2—CN$). Injection of hyposulphite of soda neutralises the toxic effects of this poison and prevents the changes in the nerve-cells. Experiment has shown that curare poisons the motor end plates, and recently, in an interesting communication, Dr. Augustus Waller showed how a very slight difference—a molecule of water—will alter the action of an alkaloid. Thus he has shown that veratrin has a special selective toxic action upon muscle, while proto-veratrin acts upon nerve. These facts, together with others which I will cite in connection with degenerative changes produced by the selective action of poisons in the production of disease, indicate a special chemical affinity of certain protoplasmic structures for certain particular poisons; and the corollary is that probably the protoplasm of every nerve structure having a different function varies to some slight degree. There is a difference which is not to be detected by chemical methods, but the varieties of which are clearly shown by the difference in their physiological reaction to an altered environment. Perhaps one of the most striking demonstrations of this selective affinity of protoplasm for particular chemical compounds is shown by the intra-vitam methylene blue method introduced by Professor Ehrlich, and which in the hands of many investigators has produced such marvellous revelations into the minute structure of the nervous system. Ehrlich found that only those aniline

dyes which contained sulphur in their composition were suitable for yielding the reaction. Examples of the special selective influence of the various poisons which produce disease are very numerous. There is a whole class of poisons which affect especially the peripheral nerves; and it is a debateable point whether in peripheral neuritis the whole neurone suffers, or whether the changes which have been found in the cells of origin of the peripheral nerves and in the spinal cord and ganglia are due primarily to the action of the poison, or whether they are secondary to the destructive effects of the poison upon the outgrowths of the cells—viz., the axis cylinder processes of the peripheral nerves. Again, there are a number of poisons—diphtheria, botulismus, &c.—in which the fatty degeneration of the muscle is far in excess of what could be reasonably attributed to the changes found in the nerves. Probably the vulnerable point of the neuro-muscular mechanism is at the junction of the nerve with the muscle. Comparative studies, however, which would show degenerative changes in the motor end plates are extremely difficult, and it is rather by inference than direct observation that we must believe the poison to act upon this structure.

The effects of a poison in producing degenerative changes may be immediate or remote, even distantly remote. Thus some poisons on entering the system may produce sudden, or almost sudden, effects—viz., strychnine or absinthe. Others produce more or less remote effects—viz., rabies, tetanus, or diphtheria; others produce distantly remote effects, as syphilis.

Again, many poisons in order to be effective must accumulate in the system—viz., the mineral poisons, lead and arsenic. Dixon Mann states that it has been shown that lead exists in the brain in appreciable quantities in encephalitis saturnina.

Selective Influence of Poisons.

The most remarkable example of selective influence which I can cite is tetanus. The bacilli are found only in the wound—they must, therefore, be comparatively few in number, yet they elaborate a virulent poison which affects particular groups of neurones. The fact that lockjaw in man nearly always occurs first shows that the poison selects the motor nucleus of the fifth nerve. This, however, is not the case in animals when poisoned

by the tetanus toxin. We do not know whether this selection is due to some anatomical condition which favours the absorption of the poison, or whether it is the result of a bio-chemical affinity of that particular group of neurones for the poison. It is remarkable that experiment has shown that the tetanus toxin if mixed with an emulsion of nervous matter before injection into an animal loses its toxicity, showing thereby its affinity for nervous matter. Goldscheider and Flatau, who have studied the changes in the nerve-cells of animals that have been injected with the tetanus toxin, describe conditions which they consider characteristic of the action of this particular poison. Examination of the cells of the anterior horns of the spinal cord shows enlargement and pallor of the nucleus, swelling and crumbling of the Nissl bodies, and fine granular disintegration of the Nissl bodies associated with swelling of the whole cell.

Marinesco maintains that in nerve-cells subjected to the action of the tetanus toxin two independent phenomena can be distinguished—one the result of the chemical combination of the poison with the cellular protoplasm, and the other the wearing out of the cell from excessive functional activity. He agrees with the conclusion of Goldscheider that there is a chemical transformation exalting the excitability of the motor neurones. There is a general consensus of opinion among authors who have worked at this subject, including those named, that the injection of tetanus antitoxin retarded these cell changes and caused a more rapid return to normal. It is only right to say that Courmon, Doyen, and Pairot, from experimental results of their own, deny that tetanus toxin produces any alteration in the cells of the anterior horns, and certainly specimens of the medulla and pons from two cases of tetanus in the human subject which I have had the opportunity of examining showed no certain noteworthy change.

Another poison, probably of microbial origin, rabies, has a special selective influence upon the medulla, although the whole nervous system is charged with the poison, pointing, therefore, to the fact that there is some special affinity of the neurones in the medulla for the poison. I have had the opportunity (through the kindness of Dr. Herbert Durham) of examining the medulla of a child who died from hydrophobia in Guy's Hospital six weeks after having been bitten by a mad dog. The greater

number of the cells of the motor nuclei of the medulla showed marked degenerative changes, indicating a slow process of coagulation necrosis—viz., uniform diffuse staining with absence of Nissl granules; there was also a great deal of nuclear proliferation in the glia substance, denoting an irritative as well as a degenerative process. Dr. Herbert Durham was also kind enough to give me the nervous systems of three animals which had been poisoned with the toxin of "bacillus botulinus"—first described by Ermenghen, who discovered the organism in unsound meat and fish eaten by people who had died with a

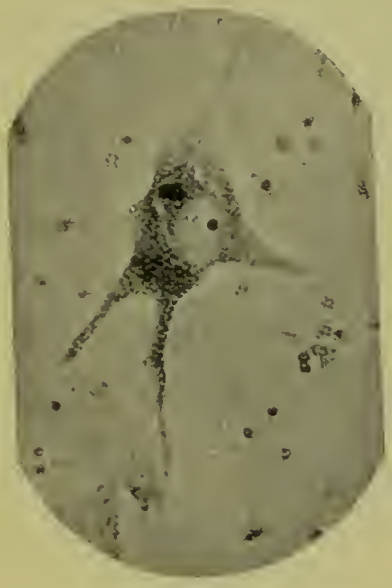


FIG. 28. Anterior horn cell of the spinal cord from a guinea-pig which died forty-five hours after injection of 0·2 milligramme of abrus globulin. Magnification 400 diameters.

characteristic group of symptoms. Such a condition in this country would probably have been called "ptomaine poisoning." The changes which I have found in the nerve-cells are similar to those described by Marinesco, who has specially studied this subject. There is a marked chromolytic change, some cells being much more affected than others (*vide* photo-micrograph, fig. 29). The poison is extremely virulent, and if a minute dose is given so that the animal does not die before the end of a week or so, the changes in the nerve-cells are not more marked than in an animal which dies within twenty-four hours. The most

noteworthy change, however, which I have found in an animal which survived eight days was the extreme fatty degeneration of the heart and striped muscles of the body (*vide* photo-micrograph, fig. 30). The liver also had undergone extreme fatty degeneration. Seeing that the peripheral nerves showed no degenerative changes, one may conclude that the poison

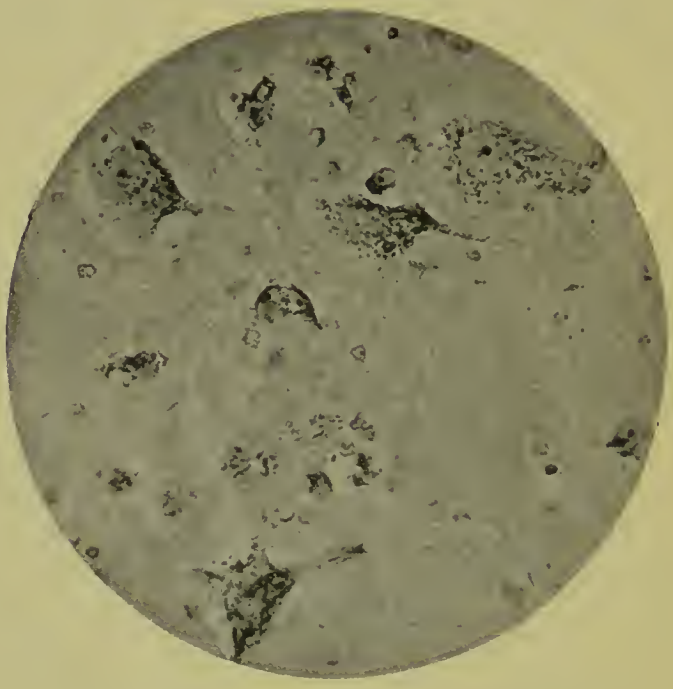


FIG. 29. A section of the anterior horn of the spinal cord of a rabbit twenty-one hours after injection of 0·01 cubic centimetre of botulismus toxin, which killed the animal. The whole of the cells throughout the central nervous system showed more or less a marked chromolytic change, as indicated in the photo-micrograph. Magnification 250 diameters.

acted more particularly upon the muscle or the nerve endings in muscle. As I have already had occasion to point out, chromolytic changes of themselves do not indicate death of the nerve-cell but rather functional depression. Seeing that there were no changes in the peripheral nerves or in the cord observable by the Marchi method, it is probable that the changes in the nerve-cells were mostly related to functional depression rather than actual destruction, and might have arisen from

circulatory failure in the central nervous system due to paralysis of the heart. Marinesco noticed that the chromatolysis generally occurred first at the periphery of the cells; as the morbid process advanced there was destruction of the achromatic fibrils and formation of vacuoles. I have not observed vacuolisation, only extreme chromatolysis. Kempner and Pollak have found similar changes in the nerve-cells, and have further observed the slow restoration of the cells to normal under the action of specific

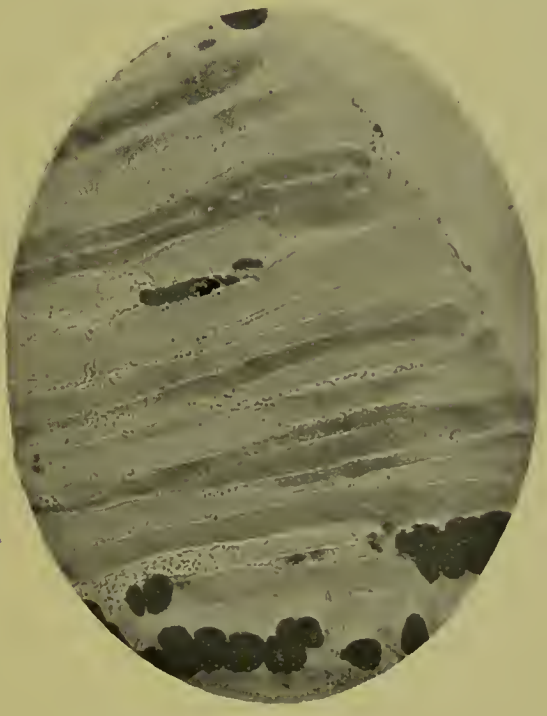


FIG. 30. A section of the diaphragm of a guinea-pig which died on the eighth day after an injection of 0·0005 cubic centimetre of botulismus toxin containing 2 per cent. of solids. The muscle was stained by the Marchi method and shows that quite one-half of the fibres have undergone acute fatty degeneration. The dense black masses are fat cells; the degenerated muscle fibres are indicated by the diffuse black staining. The musculi papillaries of the heart showed even more marked fatty degeneration.

antitoxin. Somewhat similar changes have been described by several authorities in the anterior horn-cells of the spinal cord and medulla of animals injected with diphtheria toxin. Dr. Sidney Martin separated the chemical toxin of diphtheria and produced by its injection into animals marked fatty degeneration of the muscles, which he attributed to an associated change in

the nerves. In four cases of diphtheritic paralysis in man which I have examined, I was able to find fatty degeneration of the heart muscle in all; in only one case could I find Wallerian degeneration of the peripheral nerves, and in only this one case could I find any chromolytic changes in the motor-cells of the medulla.

Abrin and ricin-toxic proteid bodies.—Dr. Sidney Martin long ago showed that the seeds of jequirity contained a proteid body which, if injected into an animal, profoundly modified the blood and caused its death. This body, abrin, together with a similar body, ricin, obtained from castor-oil seeds, were made the subject of a most valuable research upon immunisation by Ehrlich. Very small quantities of these poisons injected into animals cause profound modifications in the appearance of the nerve-cells. The Nissl bodies disappear, the cells are stained uniformly, and show a fine-coloured dust all through the protoplasm of the cell and processes. All the nerve-cells are affected, and the cause of these altered appearances would indicate a changed condition of the blood and lymph rather than a selective influence of the cells for the poison. I have examined the nervous systems of two guinea-pigs which Dr. Durham kindly sent me. One animal died forty-five hours after the injection of 0 2 milligramme of abrin globulin, and all the cells showed the appearances described (*vide* photo-micrograph, fig. 28). The other animal had been immunised, and then in the course of a week received an amount equal to sixty fatal doses without succumbing; the nervous structures in this animal showed far less change—most of the cells exhibited Nissl granules, although many showed more or less advanced chromolysis. Berkeley has studied the changes produced in the nerve-cells by ricin.

Absinthe.—Dr. Leonard Hill, while making his experiments upon the cerebral circulation, had occasion to inject animals with absinthe. He sent me the nervous tissues of these animals, and I was greatly surprised to find that changes were discoverable in the cortical pyramidal cells of animals which had died in fits within ten minutes of the injection of five minims of the poison. The cells were, however, not all equally affected; some groups of cells showed marked chromolytic change, while others showed no change. Animals that had lived two hours after the injection of a smaller dose (two minims) likewise showed unequal

effects. The cortical pyramidal cells were, however, always more affected than the motor cells of the anterior horns of the medulla and spinal cord; and one therefore naturally asks, Can we account for this by supposing that the cells have each a specific vital resistance? That this may be so is perfectly clear from the fact that such poisons as abrin, botulin, ricin, &c., produce when injected much more marked effects on some cells of the same function than on others. In the case of absinthe it must be remembered that we have to do with an oily fluid, and it is possible that really the fits may have been due to irritation caused by minute capillary emboli of an acrid and poisonous nature becoming lodged in the minute vessels of the cerebral cortex. The capillaries in the cortex are extremely small, and would favour such lodgment. Such an explanation seems possible, for if absinthe be injected subcutaneously, even in large quantities, fits are not produced (Hill). I am also indebted to Mr. Victor Horsley for the nervous system of a cat which had received two minims of absinthe intravenously injected. The animal had three fits and survived two hours. The changes in the motor cells of the brain and cord corresponded to those above described.

Figs. 14, 15, 16, 17, 18, 20, 21, 22, 26, 27, 28, 29 are photo-micrographs of preparations stained by the Nissl method. Fig. 19 was stained by the Weigert iron method. Figs. 23 and 24 were stained by the rapid Golgi method. Figs. 25 and 30 were stained by the Marchi method.

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LECTURE III.

The Chemistry of Degeneration and its Relation to Auto-intoxication.

Mr. President and Gentlemen,—Osmic acid has long been known to have the property of staining fat (including myelin) black, but owing to difficulty in penetration it could not be made use of for studying the degeneration of the central nervous system in the same way as the peripheral, although Exner[1] was enabled to show by this method the existence of fine medullated fibres (tangential system and super-radial) in the grey matter of the cerebral cortex, and Tuczek applied this method and demonstrated the important fact that atrophy of the tangential fibres of the frontal and central convolutions was the earliest and most constant morbid change in dementia paralytica. I have had the opportunity of confirming this observation in at least 50 cases by the Marchi-Pal method. This degeneration does not appear to be peculiar to general paralysis, as similar atrophy may occur in other diseases of the cerebrum associated with dementia, as, for example, in alcoholic and epileptic dementia ; it does not, however, exist in purely efferent systemic degeneration, *e.g.*, amyotrophic lateral sclerosis, although in this disease, as I shall show, the whole motor efferent system of neurones from cortex to peripheral muscle is degenerated.

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[1] Exner's method is as follows :—Small pieces of brain, one cubic centimetre in size, are placed in 1 per cent. of osmic acid for from five to ten days, cut in alcohol with a wet knife, after sticking on cork with shellac. The sections, which must be very thin, are mounted in glycerine. If they are allowed to remain in alcohol they spoil. They are best transferred on a section lifter in a drop of strongly ammoniated water. The preparation should be examined at once. The essential in this process is the use of the ammonia, whereby the neuro-keratin supporting structure is swollen up into a homogeneous mass. The finest fibres of the cortical layers are demonstrated remarkably well by this method.

The Value of the Marchi Method.

About ten years ago Marchi introduced his method of staining degenerated nerve fibres, using it for the purpose of demonstrating the degenerations which followed experimental ablations of the cerebellum performed by Luciani, and the most striking results were obtained. By this method Marchi showed a descending cerebellar system in the antero-lateral column of the same side as the half of the cerebellum that had been removed. Russell, Ferrier, and Turner, have, however, shown that this tract does not proceed direct from the cerebellum but through a relay in Deiter's nucleus. It is now the method adopted by all investigators for determining the path, not only of tracts of fibres, but of actual individual fibres, in the central nervous system. It has, in the hands of numerous investigators, served to demonstrate accurately the course and termination of nervous paths. There are a few fallacies in connection with it for the inexperienced, but if care be taken to avoid these no method is so delicate or so reliable. By this method I was able to trace the course of the fibres of Gowers's tract, which I showed to consist of three sets of fibres: one, the more numerous, terminating in the middle lobe of the cerebellum after looping over the fifth nerve and running down on the surface of the superior cerebellar peduncle; another set terminating in the corpora quadrigemina; and the third, few in number, joining with the fillet fibres and ending in the optic thalamus. By this method single fibres can be followed in their course along the whole cerebro-spinal axis, from the cortex to the lumbar sacral region when they are efferent, and from the lumbar sacral region to the optic thalamus when they are afferent. I was unable to find any evidence for the existence of a cortical fillet described by Flechsig after cutting off the posterior column nuclei in monkeys and tracing the degeneration upwards, all the fillet fibres terminating in the optic thalamus.

The Chemistry of the Marchi Method in Relation to Degeneration.

In working with the Marchi method I was struck by the fact that in the neighbourhood of a lesion vessels could often be seen with phagocytes containing black-stained particles in their

sheaths. These were undoubtedly carrying away the products of degeneration. I also found that muscles which had undergone fatty degeneration reacted to the Marchi stain—that is to say, pieces of the muscle which had been hardened in Müller's fluid, like pieces of the degenerated central nervous system, when placed in the Marchi fluid for from ten to fourteen days (one part of 1 per cent. of osmic acid and two parts of Müller's fluid), revealed fatty degeneration by the fat particles being stained black. I had long before noticed that the fat particles in degenerated muscle were stained by the hæmotoxylon when the Weigert or Weigert-Pal method of coloration was used; therefore I came to the conclusion that a non-phosphoretted fat, the result of degeneration of proteid, would be stained by either of these methods. Putting this fact by the side of another—viz., that degenerating nerves of the central nervous system, stained by the Weigert or Weigert-Pal method, appear uniformly blue throughout, whereas in a transection of the normal nerve-fibres only a ring of myelin stains blue, the central axon being unstained — the conclusion is that the proteid of the axon has degenerated and become converted into a fatty substance; but it is otherwise, as I shall now show, with the Marchi method, which really depends for the success of the reaction on the differential staining of the phosphoretted fat contained in the myelin (protagon) from ordinary (non-phosphoretted), such as olein, palmitin, stearin, &c. In sections of a normal nervous tissue stained by the Marchi method the nerve-fibres in transection present the following appearances: the central axial core is unstained, the ring of myelin is stained a greenish ash-grey colour, and degenerated fibres are stained black throughout, so that no differentiation can be seen between the myelin sheath and the axial core. It might be said that this was due to the axial core having broken up and its place being occupied by the degenerated myelin, but I have observed in longitudinal sections of nervous tissue showing degeneration in the earliest stages the axis-cylinder stained black, as well as the myelin (fig. 31). Neumann and Eichorst contend that during degeneration of the peripheral end of a cut nerve the medullary sheath and axis cylinder undergo a chemical change of such a nature that structurally and chemically it is not possible to differentiate between the two. Moreover, there are chemical reasons for supporting

this view. Examination of numbers of tissues, vegetable and animal, containing, or consisting of, simple non-phosphoretted fats, by the Marchi method showed that these fatty bodies gave the black reaction. I was lead to the conclusion that probably the myelin in the process of degeneration underwent a chemical

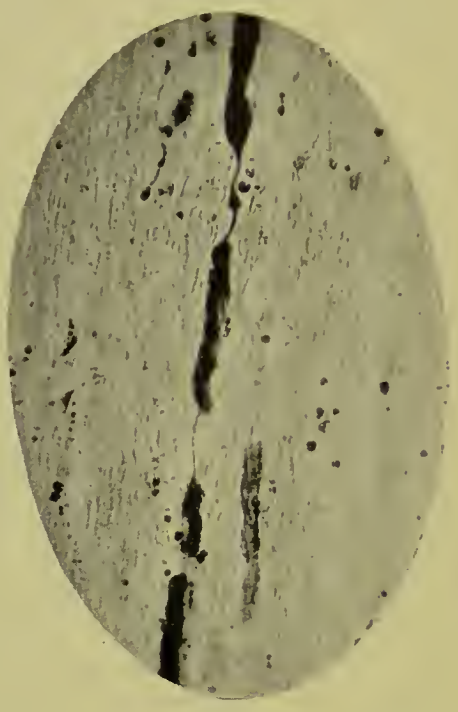

FIG. 31.—Photo-micrograph showing degenerated nerve fibre in a longitudinal section of the spinal cord ten days after experimental lesion. In places the thin axial core can be seen stained black. The greater part of it, however, is covered up by the degenerated myelin sheath, also stained black.

decomposition by which the complex phosphoretted fat was split up into simpler bodies—viz., glycero-phosphoric acid, stearic acid and choline; by the taking up of water lecithin would undergo the decomposition as shown[2]:—

[2] Liebreich and Diakonow considered that protagon was a mixture of lecithin and cerebrin, but numerous researches by Gamgee, Blankenhorn, Baumstark, Kossel, Freytag, and Ruppel have shown that protagon is a single chemical substance without, however, its precise constitution being determinable. Noll in an interesting paper refers to these researches and describes a method for the quantitative estimation of protagon. By this method he was enabled to show that protagon rapidly diminished in quan-

$$C_{44}H_{90}NPO_9 + 3H_2O_2 = C_{18}H_{36}O + 2C_3H_9PO_6 + C_3H_{15}NO_2$$

lecithin, water, stearic acid, glycero-phosphoric acid. cholin.

To prove this I took the spinal cord from a case of right hemiplegia of twenty-one days' duration, the result of thrombosis of the middle cerebral artery, and divided it longitudinally into as

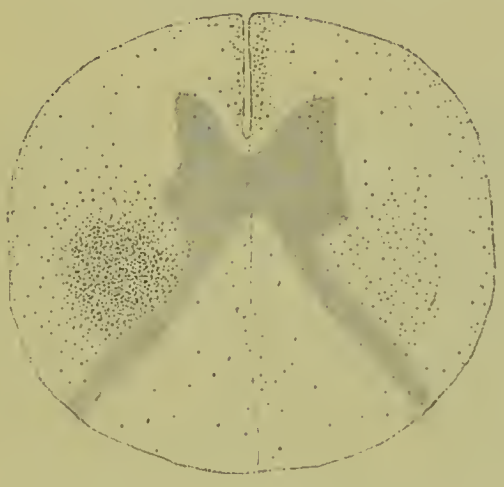

FIG. 32.—Section of first cervical segment of the spinal cord from a case of hæmorrhage into the upper part of the pons on one side, causing left hemiplegia. It will be observed that there is scattered degeneration in the homolateral pyramidal tract and also in the direct tract, but there is a very marked degeneration in the left crossed pyramidal tract. The patient died at the end of 14 days. The result of the chemical examination of the two halves of the cord is given below. Left side: ether extract, 42·1 per cent.; calculated as lecithin, 18·9 per cent.; other extractives, 23·2 per cent.; residue, 57·9 per cent.; phosphorus in ether extract, 1·72 per cent.; phosphorus in residue, 0·92 per cent.; and phosphorus in half-cord, 1·19 per cent. Right side: ether extract, 38·9 per cent.; calculated as lecithin, 22·2 per cent.; other extractives, 16·7 per cent.; residue, 61·1 per cent.; phosphorus in ether extract, 2·14 per cent.; phosphorus in residue, 0·97 per cent.; and phosphorus in half-cord, 1·38 per cent. For details of the estimation see *Archives of Neurology*, p. 346.

nearly as possible equal halves, reserving a small portion for microscopical examination by the Marchi method. The two halves of the cord were dried in a sulphuric acid exsiccator, and

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tity in degenerating nerves and finally completely disappeared. He made comparative quantitative estimations of the two sciatic nerves after cutting the nerves on one side in dogs and horses. The protagon diminished in quantity until on the twenty-eighth day it had completely disappeared. In one case he examined the central ends of the sciatic nerves and found a considerable diminution on the side of section. He also performed an experiment relating to phosphorus, and his results, he states, are in agreement with ours with regard to the splitting up of lecithin.

it was found that the right half lost the most in weight by this process. Both halves were then dried at 100° C. and extracted in a Soxhlet's ether apparatus, so that all the fatty matter was extracted. It was found that on the degenerated side the ether extract appeared like butter, whereas on the non-degenerated side it was more crystalline in appearance. The degenerated right side yielded a larger proportion *pro rata* of fatty matter than the left (fig. 32), but the phosphorus (the details of the estimation of which are given fully in the paper in conjunction with Dr. J. W. Barrett) which was obtained from the right half was less than the left. The conclusion, therefore, was that the phosphoretted fat (lecithin) had broken up in the way I have mentioned; this result I have stated in my article on the Pathology of Nutrition in the first volume of Clifford Allbutt's "System of Medicine." I have since examined another cord with the same results, and two others in conjunction with Dr. J. W. Barrett. The first results of these examinations are given in the first volume of the *Archives of Neurology*. Some of the increase of the fat cannot, however, be accounted for by the decomposition of the lecithin; it therefore probably comes from the degeneration of the proteid of the axis-cylinder process which we have seen to give the black fat staining reaction.

The Possibility of Degeneration causing Auto-Intoxication.

While examining a case of acute general paralysis with numerous epileptiform seizures I was struck by the fact that the peri-vascular lymphatic sheaths of many of the vessels were filled with vessels staining black like the Marchi reaction, and I came to the conclusion that very probably in this disease a decomposition of the myelin of the proteid matter of the nervous system occurred incidental to the degenerative process, and that the cerebro-spinal fluid, and possibly also the blood, would yield some of the products of degeneration, and perhaps the presence of such might account for some of the symptoms which occur in this disease (*vide* fig. 33). On account of the laboratory of the London County Asylums not being licensed for experiments, I was fortunate enough to obtain the co-operation of my friend, Professor W. D. Halliburton, who was good enough to associate himself with me and conduct a series of experimental inquiries relating to this subject, a full account of which has

been published in the *Philosophical Transactions of the Royal Society*. At first it was thought that choline only existed in the cerebro-spinal fluid and blood of patients who were suffering from general paralysis of the insane. This was no doubt due to the fact that in this disease choline was easily detected both chemically and physiologically, because in no other affection of the nervous system is there such a rapid and widespread

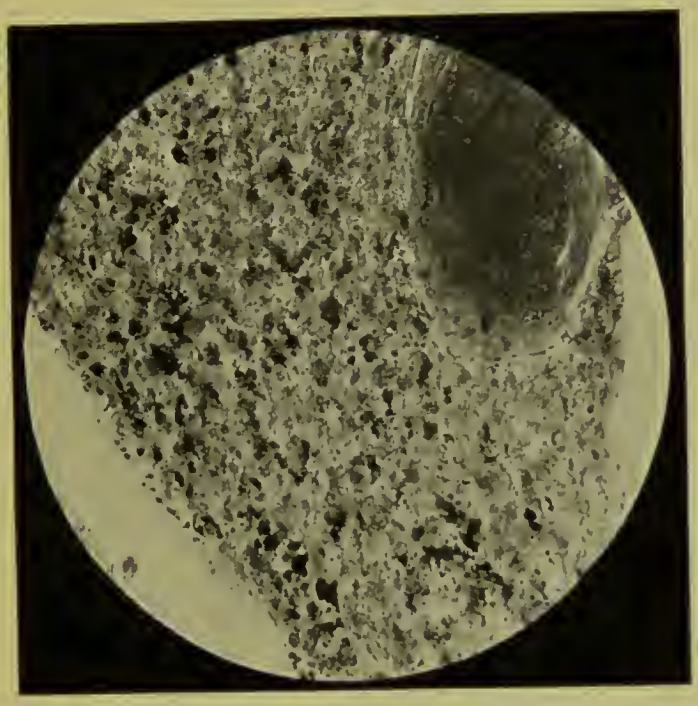

FIG. 33.—Photo-micrograph of a small vein from a case of acute general paralysis running towards the cortex with a lateral branch cut transversely, and dark in appearance on account of the contained congested blood. The section was stained by Marchi method and the whole of the external wall of the vein is seen covered with cells stained black by the fat contained in them taking up the osmic acid. Magnification 350 diameters. (*Archives of Neurology*, p. 275.)

degenerative process affecting the nervous system, but subsequent observations have shown that practically in any degenerative process affecting the nervous system, if extensive enough, choline can be detected in the blood, although normally it does not exist in sufficient quantities to be recognisable. Thus it was found in two cases of combined sclerosis and in two cases of beri-beri where the disease had been of sufficient duration to

give the Marchi reaction in the nerves; but in another case, in which the patient had died in the early stage from heart failure, there was no evidence of choline. This led to further researches, and it was found that as soon as the myelin began to undergo decomposition in the peripheral portion of the experimentally cut sciatic nerves that the blood of the animals so operated upon gave the physiological and chemical reactions indicating the presence of choline. These facts show that my original surmise was true, that the protagon splits up into simpler bodies with elimination of choline.[3] Many observers have found that extract of brain matter gave a physiological reaction similar to that of choline—namely, upon injection of a solution of alcoholic extract of brain matter a fall in the blood-pressure was produced. This was noticed by Schäfer and Oliver, Swale Vincent, and Halliburton. The latter two have continued their researches, but arrive at somewhat different conclusions: it appears, however, to me that Halliburton is right in assuming that the effect produced is due to the existence of choline, for he finds that brain extract, like choline after injection of atropine, produces a rise instead of a fall of blood-pressure (*vide* fig. 39). Again, the alcoholic extract of fresh brain-tissue yields the characteristic octahedral crystals which choline forms with platinum chloride (*vide* figs. 34 and 35). In consideration of this fact we must conclude that choline is continually being formed as a normal product of lecithin metabolism and is continually escaping into the cerebro-spinal fluid which drains into the sub-arachnoid cavity and carries away the waste products of this metabolism. This view was put forward by Professor Gumprecht at the recent congress at Wiesbaden. Although it is probable that choline is continually escaping into the cerebro-spinal fluid, either it must disappear very rapidly by absorption of the fluid or it must be in very small quantities, for normal cerebro-spinal fluid did not give the physiological or chemical reaction indicating the presence of choline. Gurlewitz, Schäfer, and others corroborate this state-

[3] Since giving the above lecture I have (with the consent of the patient) performed venesection on a young man suffering with characteristic symptoms of disseminated selerosis. The blood gave a well marked chemical and physiological reaction, indicating the existence of abundance of choline; it is very possible therefore that this may serve as a valuable test in the differentiation of this disease from hysteria.

ment. Hunt, in a recent paper, finds choline existing in the suprarenal gland. I have often thought it possible that one function of the suprarenal capsule—which Schäfer and Oliver in their valuable experiments proved to possess a powerful stimulating action upon the peripheral neuro-muscular mechanism of the arteries—is to produce a substance which will neutralise the influence of blood-pressure-lowering substances. Choline is not found in the urine, it is therefore

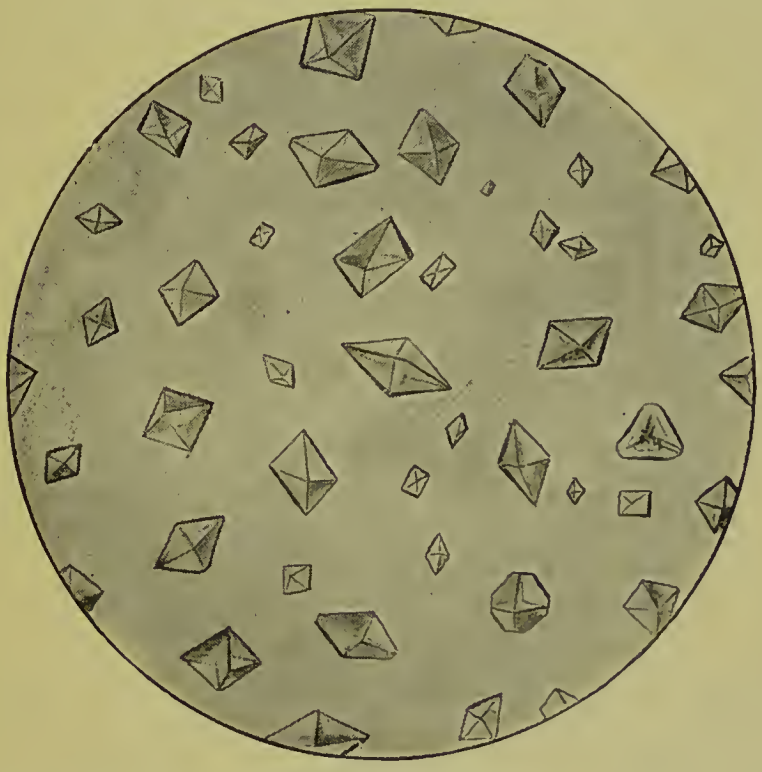

FIG. 34.—Crystals of the platinum double salt of choline crystallised from 15 per cent. alcohol.

probably oxidised into urea; it belongs to the same trimethylamine series of bodies as muscarine, neurine, and betaine, but it is not a powerful toxic substance, whereas neurine is. Many of the contradictory results which have been obtained as regards the toxic effects of choline are due to impure materials containing neurine having been used. Neurine, which is very much more poisonous than choline, has certain specific poisonous properties and acts especially upon the respiratory centre. In general paralysis and other diseases, where a large amount of

nervous tissue is undergoing degeneration, choline may exist in sufficient quantities in the cerebro-spinal fluid taken from the cadaver soon after death, or even from the living subject by lumbar puncture, to give well-marked physiological and chemical reactions indicating its presence. Two specimens by lumbar puncture were kindly forwarded to us by Dr. J. Turner, of the Essex County Asylum. It was also found in the blood taken for the purpose of treatment from patients suffering from prolonged

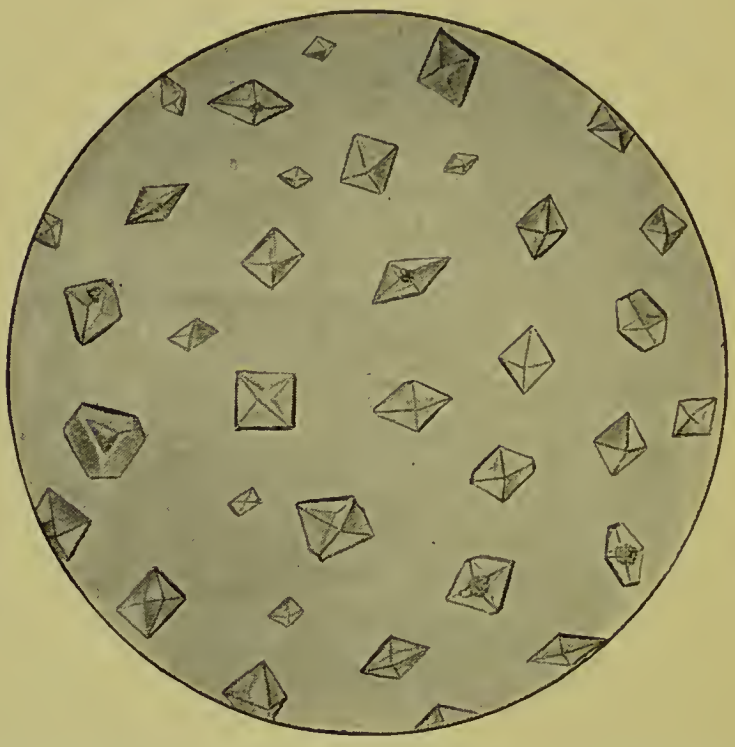

Fig. 35.—Crystals of the platinum double salt of the base separated from cerebro-spinal fluid in cases of general paralysis of the insane. Crystallised from 15 per cent. alcohol.

seizures in general paralysis and from cases of beri-beri with right heart failure and asphyxia, and in the blood of other cases, such as combined sclerosis, experimental section of the sciatic nerves, &c. We may therefore assume the premiss that choline is a product of nerve degeneration, the result of breaking up of protagon or lecithin, that it escapes into the cerebro-spinal fluid, thence into the blood in larger quantities than it can be disposed of by oxidation, and that its accumulation in the blood might

produce auto-intoxication. The principal physiological actions of choline were found to agree entirely with the effect produced by the intravenous injection of the cerebro-spinal fluid or the alcoholic extract of the blood (*vide* figs. 36, 37, 38, and 39) dissolved in normal saline solution obtained from those cases. They are as follows: A fall of arterial blood pressure, partly due to its action on the heart, but mainly due to the dilatation of the

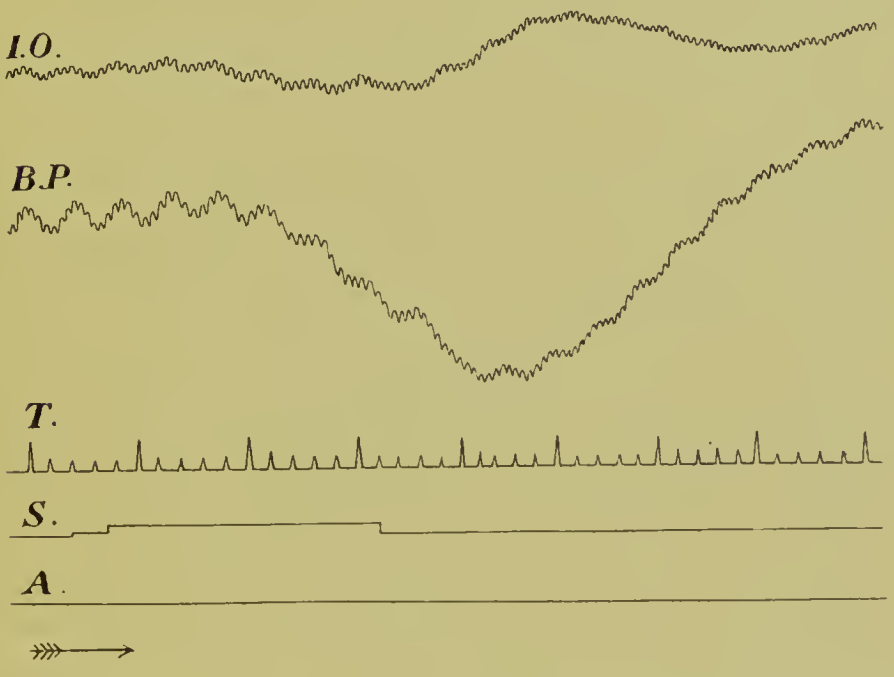

FIG. 36.—Effect of injecting five cubic centimetres of a solution of choline hydrochloride (0·2 per cent.). The fall of blood-pressure (B.P.) is accompanied by a dilatation of the intestinal vessels; this is shown by the rise of the lever of the Marey's tambour connected with the intestinal plethysmograph (I. O.) T = time record in seconds. S = signal to show when the fluid was injected, indicated by the elevation of the line. A = abscissa.

peripheral vessels, especially in the intestinal area (*vide* figs. 36 and 37). This dilatation could actually be seen to take place through the glass lid of the intestinal oncometer when the solution was injected into the vein or if the intestine were irrigated by directly allowing the fluid to flow into the oncometer. The action on the splanchnic vessels is due to the direct action of the substance on the neuro-muscular apparatus of those vessels, for after the influence of the central nervous system has been removed by the section of the cord or of the splanchnic

nerves choline still causes the typical fall of arterial pressure (*vide* fig. 39). Neurine, a very toxic substance, we did not find in the blood or cerebro-spinal fluid, although it is possible that under certain conditions, such as the existence of micro-organisms, it might be produced. It produces upon intravenous injection first a fall, then a marked rise, and subsequently a fall of blood-pressure to the normal. Neurine produces a marked effect upon

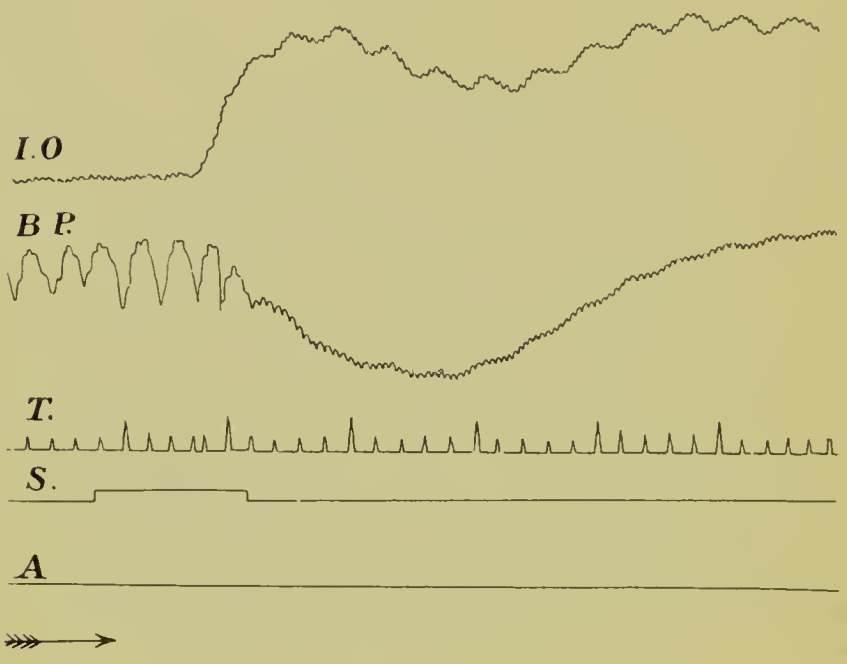

FIG. 37.—Tracing of intestinal oncometer (I.O.) and arterial blood-pressure (B.P.) in a cat. Ten cubic centimetres of cerebro-spinal fluid were injected; the same effect was obtained in the same animal by injecting two cubic centimetres of 0·2 per cent. solution of choline; the fall of blood-pressure is at first mainly cardiac in origin, for the oncometer tracing first follows the fall of arterial blood-pressure passively; it, however, soon rises, indicating dilatation of the peripheral vessels.

respiration. This is first greatly increased, but with each successive dose the effect is less and ultimately the respiration becomes weaker and ceases altogether. The animal can still be kept alive by artificial respiration. It is probable that Cervello is right in asserting that neurine acts like curare on the nerve-endings of striated muscle. Another fact of interest and importance may be the existence in the cerebro-spinal fluid of an increased amount of proteid matter. Seeing that the cerebro-

spinal fluid in the cranial cavity is greatly increased in general paralysis the quantity of proteid matter is very abundant. Examination of this proteid matter showed us that it contained a considerable amount of phosphorus; we were therefore led to believe that there was a nucleo-proteid present not found in normal cerebro-spinal fluid. As a rule we did not use the fluid itself for experimental purposes, but an alcoholic extract dissolved in saline solution, and the quantity injected (from five to ten cubic centimetres) would not contain enough nucleo-proteid to produce intravenous coagulation when diluted

FIG. 38.—Effect in a dog of saline solution of the alcoholic extract of seventy cubic centimetres of blood removed during a seizure from a patient suffering from general paralysis of the insane. There is no effect on respiration (R.), but there is a well-marked fall of blood-pressure (B.P.). In the same blood choline was identified chemically.

by the mass of blood, but in one specimen which contained a larger quantity than usual of proteid ten cubic centimetres of the cerebro-spinal fluid injected into a cat produced death by intravenous coagulation. It is therefore probable that a nucleo-proteid escaping into the cerebro-spinal fluid of the perivascular lymphatics may favour congestive stasis and even coagulation in the veins of the brain in general paralysis especially during the epileptiform seizures, when presumably the nervous tissue is undergoing disintegration. Congestive stasis in the vessels is the rule and not infrequently intravenous coagulation, and thrombosis of the large veins and even of the longitudinal sinus sometimes occurs. Thus the disintegrating nervous tissue, by

providing a substance which favours stasis and coagulation, may be the means of setting up a vicious circle whereby, owing to the circulatory disturbances, acute destructive processes of the nervous tissue are brought about. This hypothesis is supported by the fact that most of the nerve-cells in the degenerating tissue of the cortex are devoid of the normal Nissl granules.

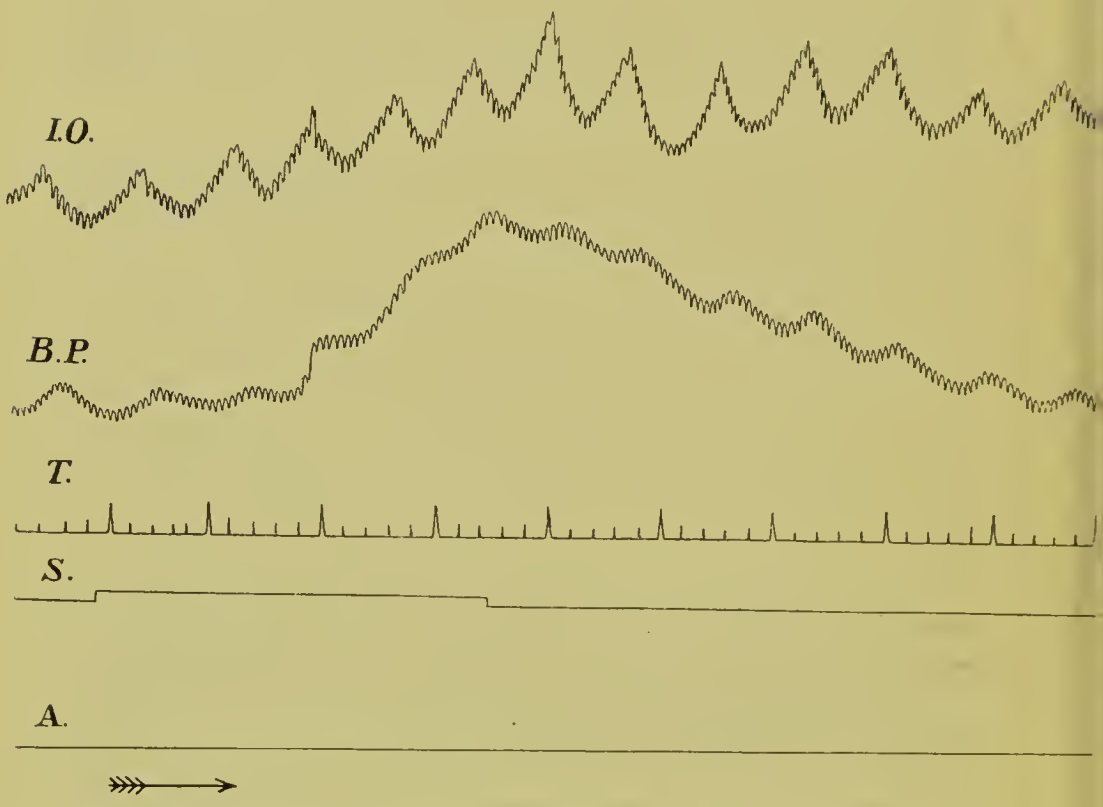

FIG. 39.—Injection of five cubic centimetres of pathological cerebro-spinal fluid in an animal anæsthetised with A.C.E. mixture, but which subsequently received an injection of atropine. It will be observed that now instead of producing a fall choline causes a rise of blood-pressure. The same effect is produced by the injection of five cubic centimetres of a 0·2 per cent. solution of choline hydrochloride.

Now it has been shown by Held that these Nissl granules are the result of coagulated nucleo-albumin, for sections of nervous tissue hardened by alcohol and treated by artificial gastric juice still show the granules and these stain in a characteristic manner. Moreover, Macallum, by his modification of Lilienfeld and Monti's molybdate method, has micro-chemically demonstrated the

existence of abundant phosphorus in these granules; we may therefore conclude that the disappearance of the same from the degenerating cells may be associated with the existence of a nucleo-proteid in the cerebro-spinal fluid. The researches of Halliburton have shown that the tissue fibrinogen of Wooldridge, which causes coagulation of the blood when injected intravenously, is a nucleo-proteid; and Halliburton has shown that the nucleo-proteid of brain-tissue, like that of other tissues, has a powerful action in producing intravascular clotting. Seeing that in no disease do we find nervous tissue undergoing such rapid and extensive decay as in general paralysis, it is quite reasonable to presume that the existence of nucleo-proteid in the cerebro-spinal fluid contained in the perivascular lymphatics may be one contributory factor in occasioning vascular disturbances and congestive stasis, especially in those regions in which mechanical conditions favour venous stasis—viz., the frontal and central convolutions. Figs. 40 and 41 show the regions where pia-arachnoid thickening and atrophy are most marked, and the area will be seen to correspond to the distribution of veins opening into the longitudinal sinus; and it will be observed that if there is a tendency to venous stasis it would most likely take place in these veins, because the blood has to run contrary to gravitation. Again, we know that the veins run into the longitudinal sinus in a direction opposed to the current, so that any conditions which give rise to general venous congestion would make themselves felt, especially in the area drained by these particular veins. Of course, it may be argued that the great anastomotic vein of Trollard has an important connexion with the lateral sinus, and that this would prevent, in a measure, such mechanical disturbances. Still, look at it as we will, we must consider that the flow of blood in the veins I have indicated is at a mechanical disadvantage compared with that of the other veins which drain directly into the torcula or into the lateral sinus. That venous congestion does play an important part in the production of the congestive, epileptiform, and apoplectiform seizures of general paralysis is shown by the fact that a brisk purge or an enema will often prevent or cut short these seizures, presumably by relieving portal congestion and general venous turgescence. If, as we have seen, choline has the property of dilating the intestinal vessels in such a marked manner, it is possible to conceive that

it may cause portal congestion and thus act as a factor in the production of venous stasis. The effect produced experimentally was only transitory because the quantity of choline introduced was rapidly diluted by the mass of blood, and probably oxidised also; yet when the whole mass of blood contains this substance in appreciable quantity continuously it means the possibility of constant toxic effect; therefore, although choline can hardly be regarded as a dangerous toxic substance, still, under certain circumstances it may serve as an additional factor in the production of complications in this disease.

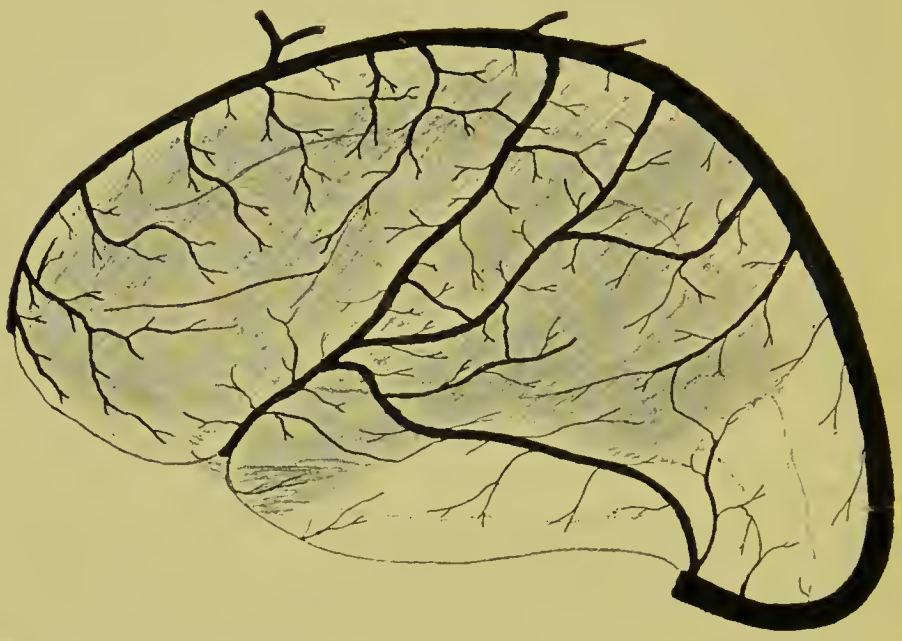

FIG. 40.—External and upper surface of hemisphere, showing distribution of veins opening into the longitudinal sinus. The shading shows the usual area of pia-arachnoid thickening. A large branch is seen running back into the lateral sinus, connecting it with the great central anastomotic vein. The lateral sinus is diagrammatically represented as continuous with the longitudinal sinus and the torcular is not shown.

The Marchi reaction applied to the central and peripheral nervous systems shows rather different results; one striking difference is the comparatively rapid disappearance of the products of degeneration in peripheral nerves as compared with the central nervous system. For example, if the posterior spinal ganglia be removed and the animal kept alive for months no traces of the products of degeneration can be found in the

peripheral nerves, whereas in the posterior columns of the spinal cord I have found well-marked evidence of the products of degeneration. Dr. H. Head, who has worked extensively on the changes in the cord and peripheral nerves, the result of lesions of the posterior spinal ganglia, has observed the same conditions. From a large experience of this method of studying degeneration produced by all kinds of lesions of the cord and brain in animals, also from disease occurring in man, I have been struck by the long persistence of the products of degeneration in the central nervous system as compared with the peripheral. Is this con-

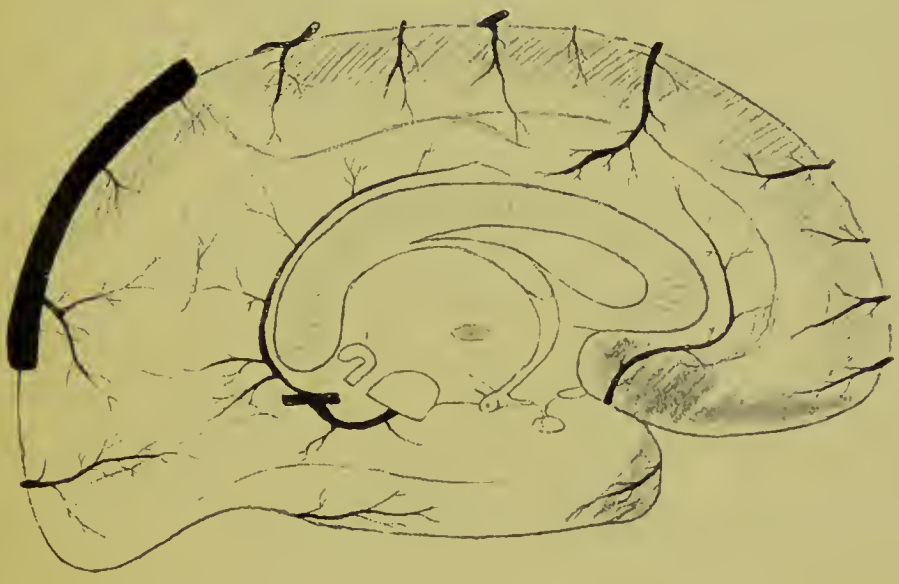

FIG. 41.—Mesial surface of hemisphere, showing the veins opening into the longitudinal sinus draining the upper portions where the thickening of the pia-arachnoid occurs. Only a small portion of the longitudinal sinus is represented. These drawings are from Testut modified to show the area of pia-arachnoid thickening and its correspondence in great measure with the area drained by veins opening into the longitudinal sinus.

nected with the anatomical difference which we know to exist between the nerve-fibres in the central nervous system and peripheral—viz., the existence in the latter of a chain of tubular cells of mesoblastic origin, forming the nucleated sheath of Schwann? And, we may ask, do these cells have a phagocytic action upon the products of degeneration, utilising the same for the formation of fresh protoplasm and myelin? And does the peripheral portion of the nerve-fibre depend solely for its nutrition

upon the central cell of origin? There is accumulating evidence in favour of the view that nerve regeneration may take place from the periphery, but there is no evidence to show that regeneration of fibres of the central nervous system (where this sheath is absent) can take place.

Two Forms of Degeneration.

There are two forms of degeneration, but both may react to the Marchi stain. They are as follows:—(1) Secondary (Wallerian) degeneration due to interruption of the axon when it is cut off from its cell of origin, as, for example, in a focal transverse lesion of the spinal cord produced by disease or injury. Tracts of fibres which have their cells of origin above the lesion degenerate downwards and are recognised by the black-stained products of degeneration mapped out in definite areas corresponding to definite systems of efferent neurones, while tracts of fibres conducting afferent impulses having their cells of origin below the lesion have a normal appearance. The converse applies to tracts above the lesion—viz., all the afferent tracts which have their cells of origin below the lesion have their limits definitely mapped out by the black-stained products of degeneration, while those with their cells of origin above have a normal appearance. Therefore, secondary degenerations, whether occurring as the result of experiment or disease, may be considered of traumatic origin and arising from conditions outside the neurone very frequently due to vascular occlusion and local softening. (2) Primary degenerations are clinically and pathologically quite different from secondary. They arise as a result of altered conditions of the blood and lymph, due generally to the introduction or generation within the body of poisonous substances, and are insidious in origin, progressive in character, and generally fatal in termination. They are influenced by hereditary or acquired tendency to nervous degeneration, and election of the particular system or systems of neurones not only constitutes definite groups of clinical phenomena, which admit of empirical classification into definite diseases, but also shows that certain poisons have elective affinities for particular systems of neurones; but the election of certain structures may also be determined by occupation and habits which induce stress on some particular system of neurones, or vascular conditions may lead to circulatory disturbances which

will determine the appearance of degenerative changes earlier and their more rapid progress in certain parts of the nervous system than in others. In connection with the latter contributory factor we have already referred to the reason why certain portions of the brain should show more atrophy and degeneration in general paralysis than others. Again, I have found the left hemisphere, which presumably is used more than the right in all right-handed people, is more often atrophied in general paralysis, for the two hemispheres in this disease are seldom of equal weight, and the left hemisphere in two-thirds of these cases weighs less than the right. We know that the speech affection is one of the most characteristic and earliest clinical phenomena of this disease; possibly this difference in the weights may be the result of excessive activity of the left hemisphere while in a process of decay. At the same time, this tendency of the left hemisphere to waste more rapidly than the right might be partly explained on mechanical principles, for venous congestive stasis might take place more easily in the left hemisphere than in the right, owing to the fact that the blood in the internal jugular vein on the right side has a more direct course to the right auricle than the left.

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LECTURE IV.

Some Chronic Toxic Conditions.

Mr. President and Gentlemen,—So far I have dealt with experiences relating to poisons producing acute or subacute changes in the nerve-cells. I shall now refer to the effects of chronic poisoning of the system, especially in reference to two factors which are the most potent, the most prevalent, and the most persistent poisons in the production of the degeneration of the neurone, and which frequently act in combination, affecting not only the nervous system of the individual but also of the offspring. Such are alcohol and syphilis.

The Close Relationship in the Etiology and Pathology of Tabes and General Paralysis.

Syphilis is the best example of a poison probably, though not proved to be, of microbial origin, which has a selective influence upon the nervous system with a remote effect; it is the most important factor in the production of two progressive degenerations of the nervous system, one affecting especially the exogenous afferent spinal neurones—namely, locomotor ataxy; the other affecting the association systems of neurones of the cerebral hemispheres, especially of the frontal and central convolutions—namely, general paralysis of the insane. A striking instance of the selective action of the syphilitic poison is shown in the fact, first pointed out by Sir William Gowers, that only in persons affected with acquired or inherited syphilis is the symptom known as the Argyll-Robertson pupil found; indeed, it is sometimes the only symptom. Seeing that this is the most common objective phenomenon in the two diseases mentioned it strengthens the presumption, based on experience, that the

syphilitic poison is the cause of the disease in the majority of instances. It is the opinion of many authorities—and I must say that my experience supports it—that locomotor ataxy and general paralysis are one and the same morbid process, affecting different parts of the nervous system. They are, in my opinion, both a primary and progressive decay of the nervous elements and are etiologically, clinically and pathologically, very closely related. At a discussion held at the Pathological Society of London I supported the view that tabes and general paralysis are one and the same disease affecting different parts of the nervous system. It was asked if this be so, how do you explain the fact that in general paralysis it is the brain, and especially one particular part, which is affected, while in locomotor ataxy it is the cord? Let us consider the effects of poisons like alcohol, lead, ergot, lathyrus, and diseased maize (pellagra). They may produce both peripheral nerve and cord changes, together with brain changes in the same individual. It is the individual, his occupation and habits, which determine the seat of the morbid process. In some cases, however, the cord symptoms, on the one hand, predominate and the brain symptoms may be slight, or even absent; on the other hand—and these are the cases of lead and alcoholic poisoning which come into the asylums and are not seen in the hospitals—we have the brain symptoms predominant and the paralytic symptoms often less defined, overshadowed by the brain affection or even absent. So it is with general paralysis. Cases come into the hospitals with Argyll-Robertson pupils, marked paresis, and speech affection, but with the mental symptoms only comparatively slightly developed. Likewise numerous cases of tabes attend the hospitals for a considerable time and then marked mental symptoms develop, when the case is certified as tabetic general paralysis. In all these degenerative diseases we have more than one factor in operation, and I quite agree with Edinger in his opinion that *stress* will determine the initial localisation of the degenerative process. I do not know that we can learn very much about these primary degenerations from experiments upon animals. However, much valuable knowledge undoubtedly has been obtained by the effects of poisons in producing acute or subacute degeneration of the neurones. Certainly animals have not been inoculated with syphilis. Tuczek, who first described the changes

in the nervous system in ergotism and pellagra, was unable to produce these degenerative processes in animals by long-continued feeding with diseased rye, nor have other experimenters been successful with injection of ergotin and sclerotic acid. Likewise, alcohol and lead administered to animals do not produce the characteristic clinical and pathological conditions found in man. Moreover, many other poisons, the products of micro-organisms, produce different effects in man to those produced in animals. The close association of tabes and general paralysis is to my mind clearly shown by the fact that there are a considerable number of cases in which it is difficult to say whether they should be classed from their clinical symptoms and morbid changes found *post mortem* as tabes with mental symptoms or as cases of tabetic general paralysis. I have seen cases in which the diagnosis of general paralysis has been made because the patients were suffering with mental symptoms indicating that disease—viz., maniacal or melancholic symptoms and delusions associated with ataxy. After a time the mental symptoms have cleared up and the case has then been called tabes. Again, I have frequently seen cases of tabes which begin with all the characteristic phenomena of this disease and then terminate in progressive dementia and paresis, dying in an asylum from general paralysis. Symptoms which are looked upon as characteristic of tabes, such as grey atrophy of the discs, are not at all uncommon in general paralysis (10 per cent.), and I have met even with symmetrical perforating ulcers (fig. 42) and Charcot's joint. I have recently examined twelve cases of the tabetic form of general paralysis in which the changes in the brain (naked-eye and microscopical) were characteristic of general paralysis and the cords showed the characteristic lesions of tabes. My experience would point to about 10 per cent. of the cases of general paralysis being associated with tabetic cord lesions. The etiological relationship of the two diseases is almost identical; both affections occur usually in the prime of life, are more prevalent among townspeople, affecting men of all grades of society, but as a rule only women of the lower and lower middle class. Again, juvenile general paralysis and juvenile tabes probably occur only in the subjects of congenital syphilis, and the sexes are affected with equal frequency. I have met with one case of the latter and thirty cases of the former with twenty-four *post-*

mortem examinations. In 80 per cent. of the cases of juvenile general paralysis a definite history or signs of syphilis were obtained. A considerable number of cases have now been recorded of married couples being affected with general paralysis. I have recently seen a man who had well-marked signs of syphilis who subsequently died from the tabetic form of general paralysis; his wife, who had healthy children by the first husband and none by this second, is now dying from general paralysis. Dr. T. Buzzard related a similar case at the discussion referred to.

FIG. 42.—Symmetrical perforating ulcers from a case of tabetic general paralysis.

SOME FACTS CONCERNING THE ETIOLOGY AND PATHOLOGY OF GENERAL PARALYSIS.

There are two types among the juvenile general paralytics; (1) in which the syphilitic poison seemed to have produced an arrest or impaired development of the higher centres, so that the child was weak-minded or imbecile; and (2) in which the child

was mentally capable, in some cases highly intelligent and active-minded. The cause of the degenerative process in most of these cases seemed to be associated with the increased psychical *activity*, which must of necessity develop after puberty, when new emotions, objects, and ambitions are awakened by the sexual instinct and the struggle for existence. That psychical activity plays a very important part in this disease as affecting adults is clearly shown by the following facts: the sufferers are nearly all townspeople with a quick reaction time, ambitious and energetic, and the first symptom of the disease may be undue mental activity approaching now and then to that of genius. It might be argued that a large number of these people are from the lowest and least educated classes; still, I am convinced that they belong to the mentally active class. Not only do we find the people affected possess mental activity but also usually sexual proclivity, and it is very difficult to decide whether the increased sexual activity so frequently met with in the early stages of this disease is a cause or an effect. But all forms of mental excitement are associated with fatigue, and too often the neurasthenic condition which precedes the more definite symptoms of the organic brain affection leads to alcoholic excesses, and it is often very difficult to decide whether a case is one of *mania à potu* or of general paralysis. The two are frequently combined, and if so the disease runs a more rapid course. The researches of Bonhofer and Trömner have shown that acute degenerative changes may occur in the cortical cells as a result of acute alcoholism; and I have found, and can therefore agree with Jolly, that in cases of alcoholic dementia there exist organic changes affecting the superficial layers of the cortex and causing atrophy of the tangential fibres. It is, then, probable that although alcohol will not of itself produce general paralysis, it will materially increase the rapidity of the progress of the disease. Kraft-Ebbing sums up the etiology of this disease in two words—"civilisation" and "syphilisation"; and he brings forward very convincing facts and arguments in favour of the important *role* of syphilis. It has been argued that in Mohammedan countries where syphilis is rife general paralysis is unknown. The recent report for the year 1899 by Dr. J. Warnock from the Egyptian Hospital for the Insane, entirely upsets this view. He states: "During 1899, 57 general paralytics were

under care out of a population of 500. The large towns furnished nearly all the cases of this disease, and syphilis was known to be the cause in 29 of the 35 cases admitted. Twenty-four of them were native Egyptians."

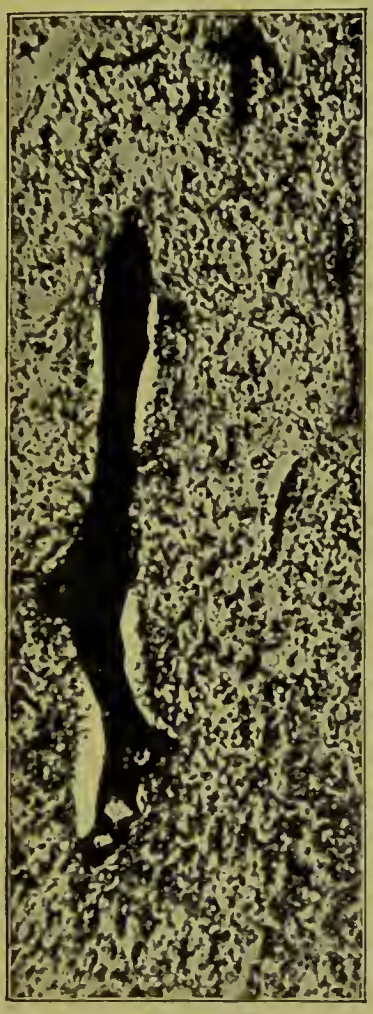


FIG. 43.

FIG. 44.

FIG. 43.—Section of ascending frontal convolution from a case of general paralysis showing engorgement of vessels, disappearance of Meynert's columns from displacement of the nerve-cells, and overgrowth of glia cells.

FIG. 44.—Section of occipital lobe from same case showing practically normal appearance of the cortex. The Meynert's columns are distinctly seen and there are no vascular changes.

Why should general paralysis be associated especially with atrophy of the frontal and central convolutions? It has already been pointed out that in these regions venous stasis is most likely to occur. Psychical activity is associated with hyperæmia of the

brain and congestion; those portions of the brain in which the mechanical conditions favour this congestion in the most marked degree would be more likely to suffer from the effects of the congestion. The whole cerebrum and spinal cord waste in general paralysis; but certain regions are earlier and more markedly affected than others—viz., the frontal and central convolutions (*vide* figs. 43 and 44). These are the regions whose veins drain into the longitudinal sinus and in which, therefore, for reasons previously mentioned, congestive stasis is more liable to occur. If it be admitted that owing (in the majority of cases) to the influence of the syphilitic poison the durability of the nervous system has been lowered, increased psychical activity will tend to exhaustion and disturbance of the normal nutritional equilibrium of the neurones. But psychical activity will cause hyperæmia and congestion of the brain, and in regions where there is a tendency to stasis the congestion may persist, especially if it leads to insomnia. A vicious circle becomes established by conditions which tend, on the one hand, to perpetual venous congestion in certain regions, and, on the other hand, to increased excitability of the neurones; these factors mutually interact.

Venous congestion (according to the researches of Waller, who has shown that CO_2 increases the excitability of nerve) may lead to hyper-excitability of those regions in which the stasis occurs. Likewise there is probably an impaired supply of arterial blood to the brain for the following reasons. The experiments of François Frank show that excitation of the Rolandic area of the cortex causes contraction of the arterioles and rise of blood pressure; observations which I have made upon the blood pressure in general paralysis by Hill's sphygmometer entirely accord with the results obtained by Leonard Hill and Craig. There is a considerable rise in the arterial pressure above the normal, and this is increased markedly during the occurrence of seizures, whether congestive or epileptiform. The blue condition of the skin and the coldness of the hands and feet of patients suffering with general paralysis suggest a small amount of blood in the arterial system and a large amount in the venous. Although we find this high arterial pressure there is seldom marked hypertrophy of the left ventricle, and I have found that if a patient has a great number of epileptiform seizures the arterial pressure falls

and right heart distension and sometimes a condition of asphyxia arise, with great engorgement of the veins, and death in consequence. The heart muscle in these cases exhibits early and often extensive fatty degeneration, due to a combination of causes—insufficient oxygenation of the blood, auto-intoxication probably from fatigue products, and increased destructive metabolism owing to the much greater resistance to be overcome. Not only the heart but also the striated muscles show this change. I could not find evidence of degeneration of nerves to account for this change, neither do I believe this to be the effective cause, seeing that exactly the same changes in heart, diaphragm, and other striped muscles have been found by me in seven cases of status epilepticus.[1] Some of the latter patients prior to the fits were in perfect bodily health. In connexion with this I may mention that the venous congestion of the brain caused by the status epilepticus produced marked changes in the cells of the cerebral cortex, changes which corresponded with the appearances presented by many of the large pyramidal cells in general paralysis and not unlike those found in experimental anæmia with convulsions. There was great swelling of the cell (œdema), disappearance or disintegration of the Nissl granules, often eccentric position of the nucleus, and dilatation of the peri-neuronal and vascular lymph spaces. Moreover, epilepsy frequently ends in dementia, and we find in such cases atrophy of the tangential super-radial and inter-radial association fibres, a condition which is always found in general paralysis even in the earliest stages before any fits occur. It is probable that atrophy of the tangential super-radial and inter-radial fibres is a constant lesion in permanent dementia. In connection with this it is interesting to note that in a case of congenital hemiplegia with epilepsy in which there was no dementia, there was no atrophy of these fibres (*vide* figs. 45 and 46). Dr. George Watson, who has looked over a large number of my specimens, reports that in 20 cases which he has examined he found the tangential fibres, the super-radial and inter-radial fibres atrophied in all the 16 cases of general paralysis, but that of these 16 none showed any recent change by the Marchi method; consequently we must suppose the atrophy was of some considerable standing, and

[1] *Vide* "Archives of Neurology," p. 493.

probably years before the patient comes to an asylum a regressive change has commenced in these latest morphologically-developed structures. Occasionally I have been able to show that the tangential fibres of Broca's convolution are more atrophied on the left than the right side when the left hemisphere has weighed less than the right. The four cases in which he did not find atrophy of the association systems mentioned were primary

FIG. 45.—Photo-micrograph, low power. Section of motor cortex of left hemisphere from a case of congenital hemiplegia of right side, stained by Marchi-Pal method. Although there was atrophy of the large pyramidal motor cells and sclerosis of the pyramidal tract, the tangential super-radial and inter-radial fibres are well developed. The patient showed no sign of dementia.

degenerations of projection systems—viz., two of amyotrophic lateral sclerosis, one of combined sclerosis, and one of universal syphilitic arteritis. In a considerable number of the cases of general paralysis there was recent degeneration of the radial fibres, especially in those cases where there had been epileptiform seizures. The perivascular lymphatics also contained the fatty products of degeneration. We can thus understand that a

number of contributory factors may arise to establish a vicious circle which is continually enlarging until a fatal termination occurs. Such factors may not only lead to rapid destruction of the neurones or nervous elements, but by irritation lead to a proliferative formation of the neuroglia cells, and we can account for the ependymal granulations almost invariably met with in this disease by the irritation caused by an altered cerebro-

Fig. 46.—Photo-micrograph of same section more highly magnified to show that the deep black line on the surface of the cortex (seen in fig. 45) consists of fine medullated fibres—these form the tangential system; beneath this in the grey matter are numerons scattered fibres snper-radial. The inter-radial are not shown, but can be seen in fig. 45 running at right angles to, and intersecting the radiate fibres.

spinal fluid. They are, however, not found exclusively in general paralysis.

General Paralysis a Primary Degeneration.

The morbid process in general paralysis has been considered by Mendel and many other authorities to be a primary meningo-encephalitis. I would advance the following reasons for considering it a primary degeneration of the neurone with secondary

meningo-encephalitis :—(1) Its relation to tabes dorsalis and the probability of its being the same morbid process due to the same cause (syphilis) commencing in a different part of the nervous system. (2) The existence of the Argyll-Robertson pupil in the majority of cases. (3) The existence of grey atrophy of the discs in a number of cases, much more frequent than can be explained by mere coincidence. The last two symptoms cannot be explained except by a primary atrophy. (4) The evidence of a wasting of the whole nervous system, but out of all proportion to the evidences of inflammation affecting some parts more than others. This wasting must be primary in the nervous system and not secondary to bodily disease, for in no cachectic disease or even in starvation do we find extensive wasting take place. (5) The thickening of the pia-arachnoid membrane is proportional to, and corresponds with, the degree and locality of the atrophy; so it is with tabes. (6) In many cases of tabes, especially those with mental symptoms, atrophy of the tangential and super-radial association fibres of the brain are found quite similar to but often in different situations to general paralysis. (7) In diseases with well-marked meningo-encephalitis, about which there can be no dispute that it is primarily an inflammatory process, we do not find this extreme atrophy. In illustration of this I would call attention to two cases of African lethargy which I had the opportunity of examining and of describing [2] for the first time the histological changes in the central nervous system. Throughout the whole central nervous system in both these cases there was evidence of a profound and widespread chronic inflammatory process. The whole of the perivascular lymphatics were choked up with mononuclear leucocytes. The pia-arachnoid membrane was similarly infiltrated, indicating the existence in the cerebro-spinal fluid or blood of an irritant poison the nature of which I was quite unable to discover, although the most painstaking efforts were made by myself and Dr. Bulloch, both *post mortem* and during life, to discover a micro-organism. The only abnormal condition that was found in the blood of these negroes, as also in a previous case of Dr. Stephen Mackenzie's (the tissues of which by his courtesy I was able to examine and observed similar histological changes), was the existence of the embryo filaria

[2] *Brit. Med. Jour.*, 1899.

perstans in the blood. The evidence of this being the cause of the symptoms or of the morbid process found in the nervous system is wholly inadequate. Although there was this chronic inflammation, yet throughout the nervous system there was far less cellular atrophy and nerve-fibre destruction, even in the most advanced case, than one meets with in quite the early stages of general paralysis. In fact, the brains showed little or no atrophy or change to the naked eye ; and microscopically there was very little disarrangement of Meynert's columns in one case. The weight of the brains showed little deviation from the normal in one case and none in the other, whereas the bodies were extremely emaciated in both cases. I think this evidence tends to show that there is a primary atrophy in general paralysis and that the inflammatory and vascular changes are secondary complications. Primary degeneration of the neurones may affect the afferent, efferent, or association systems, singly or combined, and in the tabetic form of general paralysis all three may be affected.

Primary Degeneration of the Afferent System of Neurones.

In tabes we have an example of degeneration of the afferent projection system which, for reasons already mentioned, is probably due to nutritional failure on the part of the posterior spinal neurone, by which parts most remote from the centre of nutrition undergo a regressive atrophy. The cells of origin seldom undergo marked changes unless pigmentation can be considered evidence of degeneration, but there seems to be some reason why the cells of the posterior spinal ganglia should be able to maintain a trophic independence. Possibly it may be the existence of the capsule, or possibly the cells receive stimuli from the viscera by sympathetic branches, or, lastly, it may be that they have become more or less independent of the influence of stimuli by the impulses from the periphery travelling directly across the T-shaped process. Again, after section of the posterior spinal roots I did not find any change in the posterior spinal ganglion cells. Moreover, we know that in amputation cases of long duration, although the nerves and posterior roots waste, the spinal ganglion cells undergo little change. It is particularly the central projection of the neurone that undergoes the degenera-

tive process in tabes, and from the experimental evidence above adduced this would not suffice to cause changes in the cell. The peripheral portion of the neurone—viz., the sensory peripheral nerves—have been shown to undergo regressive atrophy and degeneration from the termination towards the centre. We know that the peripheral portion of the T-shaped process is ensheathed by the hollow mesoblastic cells forming the sheath of Schwann, and which we have shown for many reasons probably exercises an indirect trophic influence upon the long axis-cylinder process.

Again, in tabes, the idea that a sclerosis of the posterior columns produced by an irritative proliferation of the glia tissue is the initial morbid process causing a secondary degenerative atrophy is the result of confusion of cause and effect. The overgrowth of the glia tissue is the result of, and proportional to, the primary progressive atrophy of the nervous elements, for we cannot suppose that the glia tissue would electively destroy exogenous fibres, leaving the endogenous intact. In support of this statement I show a photo-micrograph of the sixth cervical segment of the spinal cord of a monkey in which the third, fourth, fifth, sixth, and seventh cervical and first, second, and third dorsal posterior spinal roots were cut on the left side. The eighth cervical which especially supplies the hand was not cut. This animal was kept alive six months, and it was after a time very difficult to determine upon which side the operation had been performed, as it used each hand equally well, thus behaving entirely different to the animals which had had all the roots cut.[3] The result of this operation is shown in two bands of sclerosis in the posterior column on the side of the divided roots, with an area of normal fibres corresponding to the undivided root lying between (fig. 47).

It will be observed in this photo-micrograph of the sixth cervical segment that fine fibres are passing across the area of sclerosis to the grey matter of the posterior horn ; in not a single section of all the segments of the upper part of the cord could I find the absence of these fibres, which could only be terminal branches of the undivided eighth root. This points to the probability of the overlapping of roots of spinal segments. It

[3] Mott and Sherrington : *Proceedings of the Royal Society*, 1895.

certainly shows that sclerosis does not cause atrophy of fibres, for here is a band of fibres lying between two definite bands of sclerosis with delicate fibres passing across the sclerosed area. Obersteiner has maintained that the degeneration of the posterior columns is due to a meningitis affecting the roots at their entry, thereby compressing the accompanying nutrient vessels; but there are so many facts against this theory which will occur to everyone upon consideration that I need not mention them.

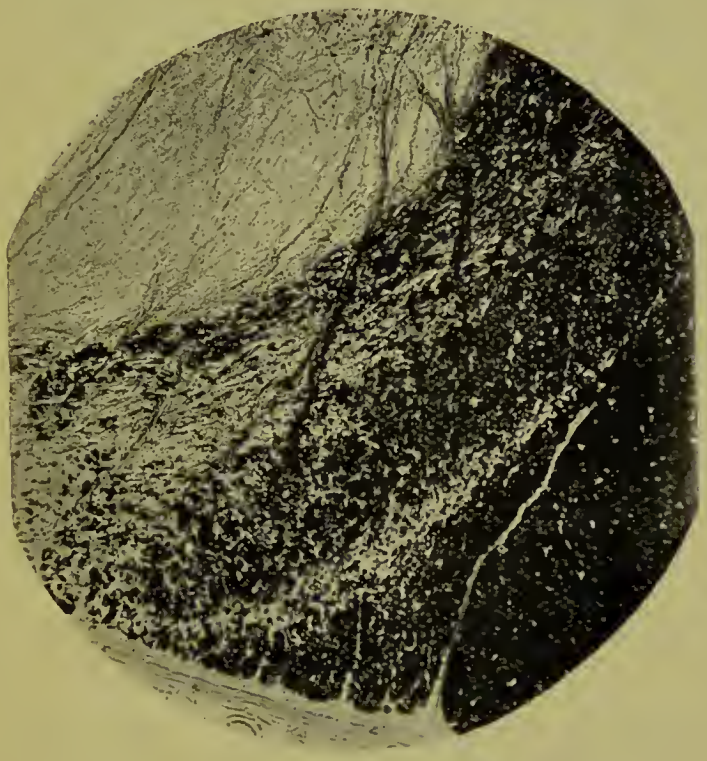


Fig. 47.—Described in text.

Suffice it to say that one does not find this same degeneration of the posterior columns in obvious cases of meningitis, syphilitic in origin. Obersteiner figures specimens stained by the Pal method showing as the fibres pass through the membranes to enter the cord disappearance of the staining. This, however, must not be taken as indisputable evidence of degeneration at this particular point, because the anterior roots sometimes show a similar defect in staining upon their emergence from the cord. Moreover, the meningitis theory does not explain the changes in the peripheral nerves met with in this disease, nor does it explain the affection of the posterior roots as far back as the ganglion,

leaving the anterior roots quite intact. That some anatomical condition of the circulation in the posterior columns may act as a contributory factor, as occurs in the frontal and central convolutions in general paralysis, is possible, especially when one considers the effects of cerebral tumour in the production of degeneration limited to the posterior columns (Hoche, Batten).

Primary Degeneration of the Efferent System.

In amyotrophic lateral sclerosis we have an example of a systemic degeneration affecting the motor efferent system of neurones from cortex to periphery. I have had the opportunity of examining three typical cases of this disease; in all three I have found degeneration of the whole efferent system comprising the cortico-spinal neurone and the spinal muscular neurone, the degeneration being limited to these neurones alone. This was pointed out by Sir William Gowers in the first edition of his manual. Certain groups of the motor spinal neurones we know from clinical and microscopical observation are affected before others—*e.g.*, the postero-external group in the eighth cervical and first dorsal segments of the cord is especially proved to be the seat of the earliest and most severe change in a large number of cases. This is a group of neurones which presides over the small muscles of the hand. I am of opinion that the morbid process in these systemic degenerations commences at the periphery of the neurones and extends back towards the trophic and genetic cells of origin, finally, in prolonged cases, causing the destruction of the cells themselves. The arguments I would advance in favour of this view are that in some cases of amyotrophic lateral sclerosis degeneration could only be followed as far as the pyramids, in others to the crus cerebri, while in other cases, published by Charcot and Marie, Kahler and Pick, and Kowjenikoff, the atrophy had extended to the pyramidal cells of the cortex. In the case referred to by the last observer there was even atrophy of the motor convolutions with thickening of the membranes; this I have also observed in one of the three cases I have above-mentioned. Again in one case I found in sections of the motor area of the cortex little foci of pyramidal cell atrophy with replacement by Deiter's cells, a condition quite similar to that which one sees in the anterior horns of the spinal cord (*vide* fig. 48). In two of the three cases which I have

examined there was not only degeneration, discoverable by the Marchi method, of the whole cortico-spinal neurones, but of the lateral branches which pass off from the axis-cylinder processes to enter the corpus callosum (*vide* fig. 49). This

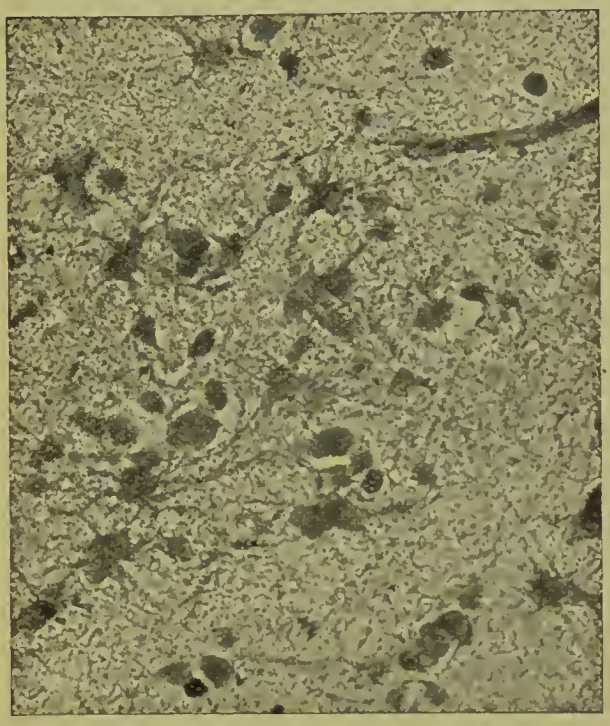


FIG. 48. — Section of lower portion of grey matter of the motor area of the cortex, showing absence of large pyramidal cells and replacement by Deiter's cells. This occurred in little isolated foci.

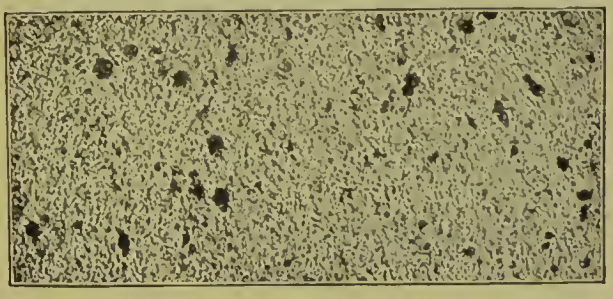


FIG. 49. — Section of the corpus callosum from a case of amyotrophic lateral sclerosis showing large black degenerated fibres in transverse section.

degeneration of the motor fibres in the corpus callosum strongly favours the primary degeneration theory of the origin of the disease being a nutritional degradation of the neurones themselves, independent of external vascular or supporting tissue

changes. Moreover, in these cases I have found that the tangential, super-, and inter-radial systems of fibres were intact (*vide* fig. 50). Now, if it were any external condition these neurones would have suffered with the motor neurones. Senator published a case of typical amyotrophic lateral sclerosis in which there was no degeneration found in the pyramidal tracts. We can only explain the symptoms by supposing that there was

FIG. 50. — Section of the superficial cortex cerebri of the Rolandic area stained by Marchi-Pal method showing the super-radial and tangential fibres intact.

interruption between the cortico-spinal and spinal muscular neurones, either a failure of junction between the two, or possibly, in view of the opinion of von Monakow and of the recent interesting observations of Schäfer, an atrophy of intermediate cells (of Golgi). Schäfer is of opinion, based upon observations made by the Marchi method on spinal cords of animals on which he had performed hemisection of the spinal cord, that the fibres of the pyramidal tract do not end in the terminal arborisation around the anterior horn (spino-muscular neurones), but are in connection with intermediate cells situated at the base of the posterior horn; if this doctrine be true a voluntary motor impulse will pass through three sets of neurones

instead of two. There is always a considerable amount of cellular atrophy at the base of the posterior horn in amyotrophic lateral sclerosis, therefore the appearances presented by this disease do not negative this theory.

Degeneration of Afferent and Efferent Systems.

Both afferent and efferent tracts of the spinal cord may undergo degeneration, giving rise to the condition known as "combined sclerosis" which is met with in various forms of grave anæmia and in pernicious anæmia, first thus described by Lichtheim and Minnich, also in ergotism, pellagra, and lathyrism. This degeneration cannot be produced experimentally in animals, and we must suppose that some auto-intoxication occurs by which a progressive degeneration affecting primarily the long tract afferent and efferent systems in the cord takes place. I have had the opportunity of examining microscopically three cases of combined sclerosis with grave anæmia, and I found that the process of degeneration was not limited to the spinal cord. In two cases which I examined by the Nissl method there were marked changes in the cortical pyramidal cells, and when examined by the Marchi method all these cases showed degeneration in the whole pyramidal system from the cortex downwards, although it was more marked and extensive in the spinal cord than in the pyramid and pons. Likewise, the cells of Clarke's column showed in two cases examined by the Nissl method degenerative changes, and both ventral and dorsal cerebellar tracts were extremely degenerated. The changes, however, in the posterior spinal ganglia were but slight, probably for the same reasons as I have mentioned in referring to tabes.

In a valuable paper on Sub-acute Combined Degeneration, that recently appeared in *Brain* by Batten, Russell, and Collier, twelve cases are narrated and seven necropsies with microscopical examinations. The authors are of opinion that the disease is a degeneration due to a toxic agent in the blood.

Polyneuritis.

Multiple polyneuritis occurs as the result of toxæmia. The poisons which give rise to the condition are numerous, but by far the most common is alcohol, and it is about this that I shall speak more particularly. Alcohol affects not only the peripheral

nerves but the brain too, where it produces degenerative changes accounting for the symptoms manifested by the patients during life. A consideration of the extent of surface of the spinal motor and sensory neurones shows that relatively the portions covered with the myelin sheath and sheath of Schwann, as compared with the rest of the neurone, are enormous. For it is obvious that the neurones supplying sensation to the soles of the feet and the motor neurones supplying the muscles of the feet are from three to four feet long, and if we admit that the trophic centres are in the cells of origin at the lower end of the spinal cord, then it is quite obvious that parts so remote from the trophic and genetic centre will suffer from nutritional failure caused by the insidious action of toxic substances such as alcohol. As the effects of the poison become more marked so the functional defect in sensation and movement travel up the legs towards the centres, so that we have in peripheral neuritis an anæsthesia progressing in the manner one puts on a stocking, and as sensation returns in recovery it proceeds as one takes off a stocking except that there is not a sharp upper border. This would quite accord with the fact that the parts most remote from the centres of nutrition are the first to be affected and the last to recover. Very probably also the parts most remote from the centre of circulation, the heart, are more liable to be affected. Thus, the extremities of the limbs are most affected as regards movement and sensation, and it seems that mineral poisons, arsenic, lead, &c., and alcohol, which are taken into the system for some time before effects are produced, act more particularly on the peripheral nerves. There is very little evidence in these cases of the poison producing interstitial inflammation, neither do we find changes sufficiently marked, as a rule, in the ganglion cells to account for the symptoms. The earliest and most obvious change is a proliferation of the nuclei of the sheath of Schwann, and this condition may be found before microscopical evidence exists of the degeneration of the myelin sheath, as revealed by the Marchi method. This does not, however, show that changes have not taken place in the myelin sheath, for the following reasons. The products of degeneration, we know from experimental section of the nerves, are rapidly absorbed and are by no means so obvious as in the central nervous system. Again, a chemical change may have

taken place in the protagon, which has not advanced to a stage in which a non-phosphoretted fat, essential for the Marchi reaction, has been produced. We know that for at least four days after section of the nerve the Marchi reaction is not given, and yet we have no reason to believe that protagon has not been undergoing a chemical change during that period. Again, the nerve fibres are not all affected simultaneously, some fibres being affected more than others. It may be asked, if the poison,

FIGS. 51, 52, 53, and 54 are photo-micrographs of cells of the anterior horns of the lumbo-sacral enlargement from a case of a woman with severe alcoholic paraplegia with extensive muscular atrophy and degenerative changes in the muscles and nerves of the legs. Magnification 600.

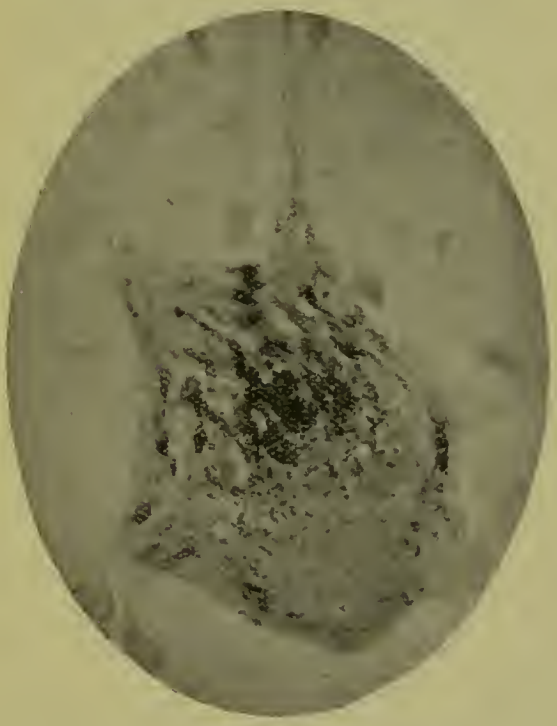


FIG. 51 shows a cell with commencing chromolytic change.

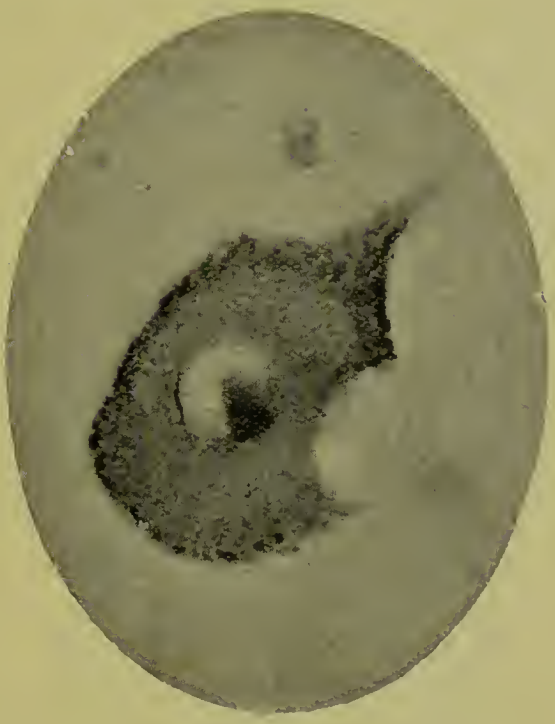
which has been accumulating in the system and producing its toxic effects on the nervous system, acts upon the whole neurone, why are changes not seen throughout the whole neurone? and why should the poison not be the effect of irritation of the chain of tubular mesoblastic cells which surround the axis-cylinder process of the neurone? If it were so there is no reason why it should not affect the nerves of all parts of the

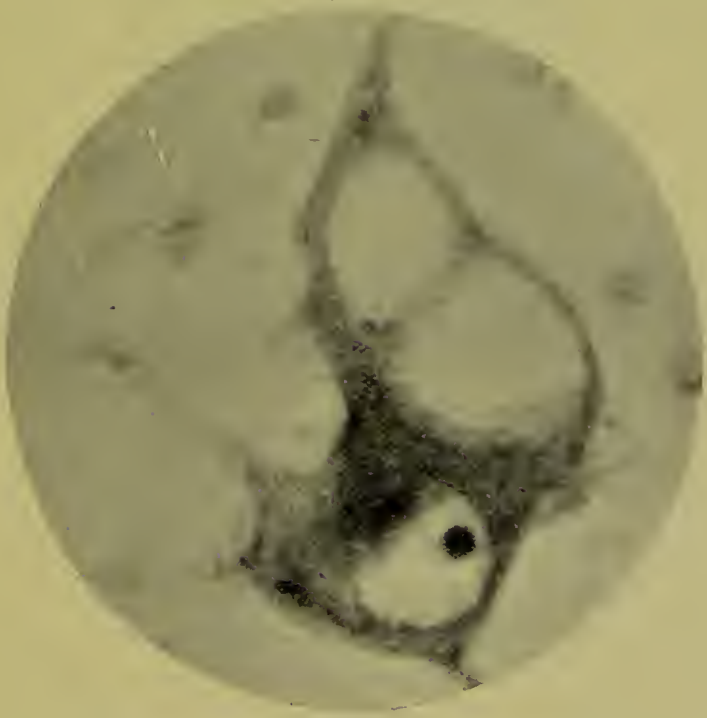
body equally. I conceive that this proliferation of the nuclei of the sheath of Schwann is due to a disturbance of the normal physiological nutritional inter-relationship between the neurone and the cells which ensheath its axis-cylinder process. It is a vital reaction on the part of these cells to the progressive nutritional failure of the neurone which will eventually terminate in destruction of the essential conducting axis-cylinder. In fact,

FIG. 52 shows a cell with advanced chromolytic change and eccentric nucleus. Both of these cells resemble the appearances presented by cells after section of a nerve, and the change may be due to the morbid process having caused destruction of their axis-cylinder process. They, however, are capable of regenerating the axis-cylinder process, the same as may occur after section of a nerve.

we know that this takes place when a nerve is cut, and it is a provision for repair; therefore it is wrong to look upon this proliferation of nuclei of the sheath as evidence of irritative effects of the poison, but rather as an attempt to repair the destruction caused by the poison.

In three cases of alcoholic neuritis which I have lately examined in conjunction with Mrs. Hamilton Williams, M.B.,





FIGS. 53 and 54 show, on the other hand, morphological changes indicating death of the trophic and genetic centre. We see in fig. 53 a concavity on one side indicating rupture of the nuclear membrane, and in fig. 54 there is so much vacuolation of the protoplasm of the cell as to indicate its destruction.

it was found that many of the nerves did not show very marked evidence of degeneration by the Marchi method; there was, however, considerable nuclear proliferation of the sheath of Schwann, especially marked in the nerves of the lower extremities. In one case in which there was complete paraplegia the ganglion cells of the lumbar-sacral spinal cord showed well-marked chromolytic changes; the Nissl granules in many of

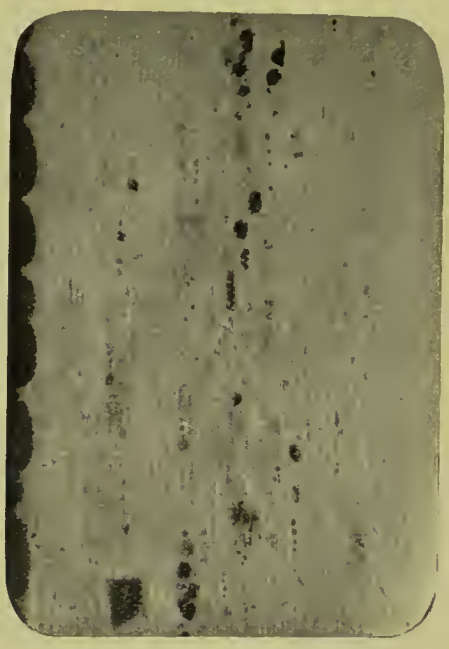


FIG. 55 is a section of the external popliteal nerve, stained by Marchi method. The black degenerated myelin is not very abundant because it has in great part been absorbed, but other stains—*e.g.*, Stroebe—show that hardly any healthy fibres exist. This preparation is from the same case as the cells described above. Magnification 200.

the cells of the anterior cornua had entirely disappeared; the nucleus was eccentric and the processes broken off; and some of the cells were vacuolated (*vide* figs. 51, 52, 53 and 54). Marked degenerative changes were also observable in nearly all the nerves of the limbs by the Marchi method (*vide* fig. 55).

From previous experience and from the electrical reactions which the muscles gave during life I should conclude that a great number of the cells would recover under favourable circumstances. The changes in most of the cells resembled rather the condition which one would find after section of a

nerve, the reaction phase, mentioned in Lecture II.; in fact, when we consider it, the condition is really very much the same as that produced by section, for the axis-cylinder processes of the sensory and motor nerves have in advanced cases died for a considerable part of their extent, but under favourable circumstances, especially if the poisonous influence be removed and the nutrition of the muscles be maintained by appropriate treat-

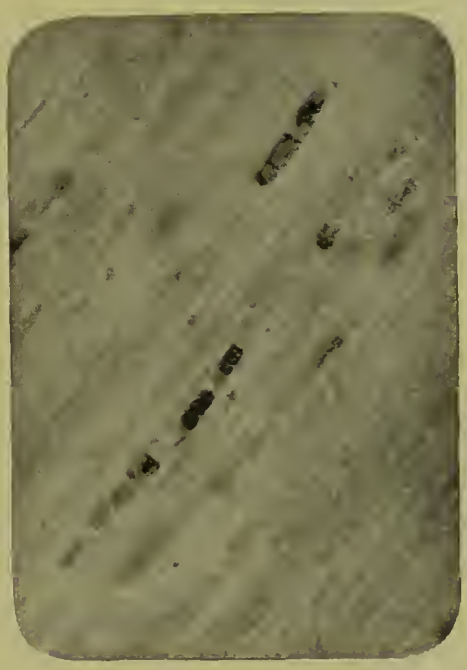


Fig. 56.—Section of the vagus nerve from a case of acute alcoholic neuritis with hæmorrhagic encephalitis and dementia. The patient suffered with very marked signs of cardiac failure and died comparatively suddenly. Marked fatty degeneration of the heart was found *post mortem*. The section stained by Marchi method shows fine medullated fibres undergoing degeneration. Magnification 600 diameters.

ment, there is no reason why, the same as in section of a nerve, regeneration should not take place. The great thing to remember is that the joints should not be allowed to become stiff or the muscles inactive. Passive movements, massage, and galvanism will stimulate the neurones and hasten regeneration, for we have already had abundant evidence to show the important influence stimulus exercises upon the metabolism of the neurones, and the degenerating and atrophic effects of non-stimulation. In two of these cases, in which there was marked

fatty degeneration of the heart, we found fatty degeneration of the fine myelinated fibres of the vagus (*vide* fig. 56).

Examination of the brains of all three cases showed a certain amount of atrophy of the tangential systems of fibres, accounting for the dementia which existed in all three cases. There were also changes revealed by the Nissl method in the cortical pyramidal cells, but seeing that there was no degeneration discovered by the Marchi method in the spinal cord we cannot assume that these were more than of a functional nature. In one case there were marked congestion and microscopical intra-cerebral hæmorrhages. The condition of the cortex could not be mistaken for general paralysis, for there was not the same overgrowth of glia cells or atrophy, nor was there the same disappearance of Meynert's columns so characteristic of the latter disease.

Relation of Stimulus to Degeneration of the Neurone.

Structure and function are mutually reciprocal and inter-dependent, and we know that a structure which is not used will gradually lose its function, while its nutrition will also suffer and in time atrophy may occur. Consciously and unconsciously a continuous stream of impulses is pouring into the nervous system from without by the sensory channels, which are the avenues of experience and intelligence, and our bodily and psychical life depends upon the existence of such stimuli.

Excess of normal stimulation of itself is seldom the cause of organic disease, although we have examples of psychomotor paralyses in the palsy affecting scriveners, typewriters, pianoforte players, violinists, hammer-men, &c., but whether this is due to an actual degeneration or to a functional depression is not known. If, however, by excessive exercise such a disturbance can take place without any other apparent cause, then undoubtedly stress acting upon structures in a state of nutritional deficiency will lead to a disturbance of the normal physiological equilibrium and a progressive degeneration of those structures which are most remote from the centre of nutrition. Increased functional activity of a part, however, is associated with increased blood-supply, and if the blood contains a toxic substance, a larger amount of that toxic substance will be carried to the functionally active part, so that whatever benefit might arise in the way of

repair from the additional amount of blood will be neutralised by the excess of poison. Numbers of instances have occurred in my experience in which stress seemed to determine the seat of the degenerative process. I will give a few illustrations. (1) A policeman who was affected with tabes commencing in the arms turned out to be a mounted policeman, and when I pointed out to the students the unusual situation he immediately volunteered the information that the pains began in the arm in which he held the reins; (2) a case of amyotrophic lateral sclerosis affecting a cooper began in the muscles of the right arm with which he wielded a four-pound hammer; (3) a man who had alcoholic dementia, paralysis, and wasting of the muscles of the upper extremities, the lower being unaffected, was shown to me as a case of progressive muscular atrophy. I found that he was a porter, and the symptoms he presented were determined by his occupation of carrying boxes all day on his shoulders. This patient completely recovered. I will not detain you with a number of further examples, but asylum experience only too well demonstrates the importance of undue mental excitement in causing degeneration of the higher structures of the brain, as in general paralysis. Professor Edinger has emphasised the important influence of stress in determining the seat of nervous degeneration, and his philosophical writings on the subject are worthy of careful consideration; he has, too, endeavoured to prove it experimentally.

Voss was unable to produce degeneration in the spinal cord in rabbits, guinea-pigs, and dogs by injections of pyridine sufficient to produce a severe anæmia; but Edinger repeated these experiments, varying them by inducing stress upon the nervous system by various means, one of which was to place the animals (rats) in a wheel cage. He claims then to have shown: (1) that abnormal stress can produce in animals a degeneration of the posterior columns; (2) that it is possible to produce a predisposition by artificial anæmia by which the influence of stress of much less degree and of much shorter duration can cause this posterior column degeneration; and (3) that this disease stands in close relationship, both as to localisation and cause, to the tabetic degeneration of the posterior columns in man.

Relation of Heredity to Degeneration of the Neurone.

Of all the causes of nervous disease hereditary predisposition stands pre-eminently first. It may be paternal, maternal, convergent, from grandparents, or, according to Weissmann's theory of the continuity of the germinal plasm, there is no limit to the remoteness of the origin of a neuropathic taint. This doctrine must have been known to the high born Romans who carried the masks of all their ancestors upon public occasions. In fact, in Lucretius it is stated: "Sometimes, too, the children may spring up like their grandfathers, and often resemble the forms of their grandfather's fathers, because the parents often keep concealed in their bodies many first beginnings mixed in many ways, which first proceeding from the original stock one father hands down to the next father, and then from these Venus produces forms after a manifold chance and repeats not only the features but the voices and hair of forefathers; and the female sex equally springs from the father's seed, and males go forth equally from the mother's body, since these distinctions no more proceed from the fixed seed of one or other parent than our face and bodies and limbs. Again, we perceive that the mind is begotten along with the body and grows up together with it and becomes old along with it." The history of the Roman emperors from Julius Cæsar, one of the greatest geniuses the world has seen, but an epileptic, shows how the endeavour to keep the sacred Julian blood for the dynasty culminated under the influence of a depraved environment in the criminal madness of Tiberius, Messalina, Caligula, and Nero. Strictly speaking, it is the tendency to nervous disease rather than the disease itself which is inherited, and this is frequently spoken of as neuropathic or neuro-psychopathic taint. There are, besides, a number of inherited diseases which, although rare, are of great interest, inasmuch as they affect members of a family, the disease frequently commencing in each individual at about the same age. These are termed "family diseases" and include hereditary ataxia (Friedreich's disease), amaurotic idiocy, hereditary chorea, and paramyoclonus multiplex, an interesting family of cases of which I have recently seen. Two boys and two girls were affected with epilepsy and this clonic choreiform spasm of the muscles; in each it commenced at the age of fifteen years.

There was no direct hereditary history in the parents of any nervous affection, but an uncle suffered from epilepsy. Presumably, therefore, ancestral germinal plasm possessed the neuropathic predisposition, which possibly under some influence which I was unable to ascertain—*e.g.*, some acute specific fever affecting the members of the family, or possibly alcoholism or syphilis in the parents—had supplied the contributory factor to develop the disease.[4] In a healthy nervous system we must suppose that the balance of potential is high, and that the sense of fatigue is the natural indication for sleep and repose by which nervous energy may be recuperated. The neuropath may be conceived to possess in some portion of his nervous system communities, groups, and systems of neurones, either of defective durability or with an inherited low potential, readily becoming exhausted and especially liable to functional depression, and which under the influence of contributory factors, such as toxic conditions of the blood or undue stress, undergo premature degeneration. To explain the inherited neuropathic tendency morphologically we may suppose that there is an inherent defect in the germinal plasm which is concerned in the formation of the neurones.

Certain acquired conditions in the parents, affecting them especially at the time of conception, are liable to produce this defect in the germinal plasm; they are acute and chronic alcoholism, syphilis, and tuberculosis. Statistics by Mr. Tredgold relating to 40 cases of congenital imbecility, although not numerous, are valuable because reliable, and in course of time, when he has completed the investigation of this question in all the London county asylums, as he has done at Claybury Asylum, will be of still more value. As far as they go they show that the most important cause of congenital imbecility is inherited neuropathic taint (70 per cent.), generally in some form of insanity,[5] but that alcoholism, syphilis, and tuberculosis are important

[1] I have since found out that two of these children had scarlet fever when young; as there is very few years' difference in their ages, it is very possible that all may have had scarlet fever.

[5] It is very interesting to note that two of the cases of imbecility with congenital syphilis have become juvenile general paralytics, and in neither of these cases was there a family history of insanity, which is independent corroboration of my observations, as neither of these cases are included in my 30 cases.

contributory factors. My own researches on juvenile general paralysis, of which I have now had the opportunity of examining 30 cases, show: (1) that the disease affects both sexes equally;

FIG. 57.—Case of juvenile general paralysis from which the preparations shown in figs. 44 and 45 were made. The disease commenced with fits at the age of eight. Photograph shows Hutchinson's teeth and rhagades round the mouth.

(2) that it may commence at any age from 8 to 23 years,[6] according to my statistics; and (3) that in 80 per cent. of the cases there were either undoubted signs or history of congenital syphilis

[6] It is possible that some of the cases occurring in adults in which no history of acquired syphilis can be obtained may still owe the disease to an inherited taint. It is not necessary that they should show external signs of syphilis, for many of the cases which I have recorded were proved to be born of syphilitic parents, although manifesting themselves no external signs of disease. A case of general paralysis died at Banstead Asylum which was under the care of Dr. Percy Smith at Bethlehem. The woman had characteristic signs of congenital syphilis, but the disease did not manifest itself until she was 28 years of age.

and that in 20 per cent. it could not be excluded. Therefore we may assume that the effect of syphilis on the germinal plasm on one or both of the parents is the essential cause. In the greater proportion of the cases I was unable to obtain a history of insanity or nervous disease in the family, although it was remark-

Fig. 58.—Case of tabetic form of juvenile general paralysis which died, aged 20 years, three months after onset of symptoms. The photograph shows characteristic teeth.

able that in 4 of the cases, and also in 1 hereditary case of tabes, the fathers suffered with general paralysis. The notes of their cases give no evidence of their having acquired syphilis, yet in 4 out of the 5 cases there were distinct and well-marked signs in their offspring. From a very careful study of the family histories of these cases I was led to believe that the germinal

plasm of the parents, particularly of the father, may be very unequally affected by the syphilitic poison, and it seemed to me that the inherited syphilis was not infrequently the result of spermatic infection only. Many of the mothers never had any illness that they knew of, yet some of their children showed syphilitic teeth, chorio-retinitis, rhagades, and other characteristic

FIG. 59.—Photograph of congenital imbecile with depressed bridge of the nose. He also had Hutchinson's teeth. A brother who died from juvenile general paralysis showed no such external signs.

signs, while other children appeared perfectly healthy. Generally, however, the history was — miscarriages, still births, syphilitic children, and healthy children in succession. In one family there were three children; the eldest had no external signs of congenital syphilis, but a syphilitic liver was found *post mortem*. He was an able-bodied seaman, but at the

age of 20 years broke down with general paralysis. I consider that this was induced by stress, for he was on duty in the Mediterranean just at the Fashoda crisis, and the disease commenced by a fit. The next brother had a characteristic syphilitic nose and teeth, but was earning his living as an artisan. The youngest boy is an imbecile in an asylum (*vide* fig. 59), with characteristic objective signs of congenital syphilis. Another family was interesting in this respect that the eldest daughter of a mother who gave a history of infection showed no signs of syphilis on the body yet died from general paralysis. The next daughter presented well-marked external signs, but at present is healthy otherwise. The majority of the 30 cases gave some interesting details bearing upon this question. Another factor which seemed to have an important bearing upon the occurrence of general paralysis in children of parents suffering with syphilis was the existence of chronic alcoholism in one or both the parents. Thus we see impaired vitality of specialised structures may result from devitalising influences acting upon the germinal plasm of one or both the parents. With regard to the toxic influence of alcohol on the nervous system I have been particularly struck with this fact, that although at least 20 per cent. of the people admitted into the London county asylums yield a history of intemperance as the cause of their mental symptoms, yet I only once remember seeing in the *post-mortem* room of the asylums a case of well-marked cirrhosis of the liver with ascites. That was in the case of a person celebrated in the police-courts who was convicted nearly 400 times of drunkenness before she was found to be certifiable as incapable of taking care of herself. One must suppose, therefore, that these people who come into the asylum are very susceptible to the toxic influence of alcohol, and long before they could drink sufficient to produce cirrhosis of the liver symptoms of alcoholic poisoning of the nervous system arise. In fact, it would rather show that a person who can drink sufficiently long to get a hob-nailed liver has inherited a nervous system of unusual stability. To the mentally unstable alcohol is a poison, and I have been particularly struck with the fact that it acts even in moderate quantities as a poison on women at the climacteric period when potential is low in the nervous system. Another class of individuals of low potential to whom alcohol is unquestionably dangerous is the neurasthenic.

The sense of fatigue, whether of mind or body, is physiological and protective. It should be responded to by rest; but the active-minded town-dweller who is suffering from nervous exhaustion takes spirits to enable him to make up the deficient energy. He draws, so to speak, a bill on his health, which must always be renewed at a higher rate of interest. My own observations and those of Mr. Tredgold, the technical scholar, entirely agree with the observations of numerous authorities who have shown that epilepsy, insanity, imbecility, idiocy, mental weakness, and loss of moral control and will power, are frequently the heritage of children born of drunken parents.

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